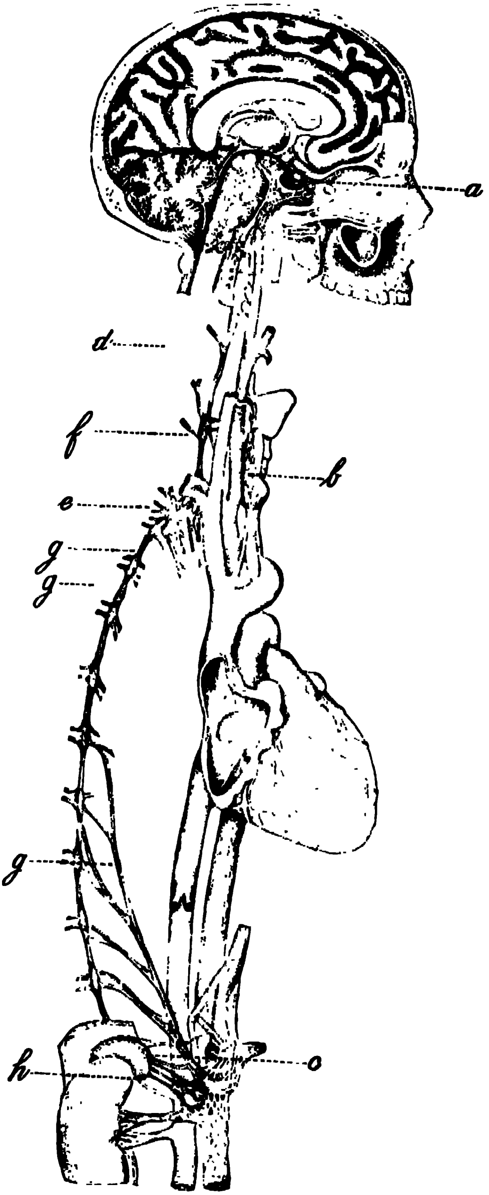

THE INNERVATION OF THE ADRENAL SYSTEM. [Sajous.]

a, Pituitary body containing adreno-thyroid center. b, Thyroid gland, supplied by nerves e, f, derived from the pituitary. c, Adrenal nerves h derived from pituitary body via the medulla, cervical cord d, spino-sympathetic branches and splanchnic g, g, g.

THE INTERNAL SECRETIONS

AND THE

PRINCIPLES OF MEDICINE

BY

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VOLUME FIRST

WITH THIRTY-SEVEN ILLUSTRATIONS

TENTH REVISED EDITION

PHILADELPHIA
F. A. DAVIS COMPANY, Publishers
1922

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Retired Govt Asst surgeon &
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DEDICATED TO THE MEMORY OF

BROWN-SÉQUARD

PREFACE TO THE TENTH EDITION.

NEARLY two decades have elapsed since the author, in the first edition of the present work, earnestly urged the American profession to realize that the ductless glands, thought by many at the time, to be either vestigial or at least useless organs even though much valuable study had been devoted to them in Europe, carried on bodily functions which would ultimately transform the whole field of practical medicine. Only now is it beginning fully to be recognized that medical progress as a whole has been handicapped through the non-recognition of these structures, which steadily are asserting their right to be classed with major organs, the heart, lungs, liver, etc., upon which all our labors have so far reposed. Their absence has seemed especially obscuring precisely where our rôle as physicians has demanded the greatest light, *e.g.*, the pathogenesis of disease and therapeutics.

So emphatically has the connection between the internal secretions and commonplace diseases—those met everyday in practice—asserted itself recently that even though the preceding edition, the ninth, appeared but one year ago, it was deemed urgent, owing to the material aid it would afford, to issue a new edition in which additional information would be furnished.

The newer matter is incorporated mainly in the first volume in the first and seventh chapters. These contain, in addition to the many diseases either described in full in both volumes, or summarized in the supplement beginning on page 1825, or referred to in the section on Organotherapy, beginning on page 700—about two hundred disorders altogether—an analytical review based, in most instances, upon the author's own experience in over sixty diseases. As these include several of the death dealing morbid processes with which mankind has to contend, stress need hardly be laid upon their importance.

It is shown therein that the author's interpretation of the functions of the main endocrins, the adrenals, thyroid, pituitary and pancreas, as first described in the present work in 1903, has not only stood the test of time, but that they alone harmonize the views of investigators whose data, when compared, are thought to be discordant. The rôle of the adrenals and the aid their preparations afford are indicated in many disorders. As regards cardiac disorders the newer matter belonging solely to the practical field includes: The senile heart, the arrhythmias, the adreno-cardiac failure of infections, the neurocardiac asthma of masturbators, the adolescent heart, auricular fibrillation, auricular flutter, heart block and sinus arrhythmia; in respect to pulmonary disorders: senile pneumonia—which contributes greatly to the mortality of lobar pneumonia because the importance of the adrenals in its pathology is disregarded—bronchial asthma: as to the renal system: anuria, acute and chronic nephritis, ascites and serous effusions; as to the general infections: Asiatic cholera, choleraic diarrhea, typhoid fever, pneumonia, bronchopneumonia, influenza, pernicious malaria, scarlatina, measles, septicemia, erysipelas, anthrax and gaseous gangrene.

The defensive rôle of the thyroid, now fully recognized in Europe, but neglected in this country to the great detriment of many sufferers, is emphasized by recent contributions to the literature of the subject. Besides the familiar endocrinopathies of the myxedematous type, the influence of the organ and its preparations upon migraine, urticaria, eczema, enuresis, catarrhal disorders, alopecia, metrorrhagia, leucorrhea, abortion, rheumatism and arthritis deformans are reviewed. The importance of the thyroid in pulmonary tuberculosis and the possible prevention of this disease by timely intervention are emphasized anew on the basis of additional evidence.

The participation of the pancreas in the defensive functions is not only shown to have been sustained by others, but also to explain, when acting in harmony with other endocrins, the thyroid gland particularly, various obscure processes, beneficial if acting within normal bounds, as exemplified by fever, harmful when its efficiency exceeds certain limits, as in hyperthermia. This morbid process, long ago urged in the present work, is then shown to prevail in endocarditis and its evil consequences, valvular disorders, and many other diseases such as pleurisy, pericarditis, peritonitis, diabetes mellitus and insipidus, hepatic cirrhosis, acute yellow atrophy, amyloid liver and similar conditions, some of which are amplified in the seventh chapter. The latter also contains a comprehensive study of dementia præcox which owing to the inefficiency of curative measures, is sending fifteen thousand children to the asylums every year—and reviews of other disorders of the nervous system, such as tabes dorsalis, acute myelitis, etc., all in their relations to the endocrins and their treatment on non-empirical lines, the author's paramount aim.

In addition to the above, various adjustments and lines of evidence have been introduced in the second volume. Both volumes, moreover, will be found to contain all the new features introduced last year in the ninth edition, the preface of which follows the present one, so as to enable the reader to gauge the rapidity with which the endocrins are asserting their elucidative influence upon general practice and therapeutics.

CHARLES E. DE M. SAJOUS.

Philadelphia, Dec., 1921.

PREFACE TO THE NINTH EDITION.

IN the first edition (1903-1907) the author submitted personal interpretations of the functions of various endocrin glands which seemed to him to warrant the prediction made at the time, that these organs would modify profoundly our conception of practically all diseases. The bearing of this prediction was illustrated by analyzing the symptomatology, pathogenesis and treatment of many diseases, and therapeutic agents. Until then, the diseases of the ductless glands themselves, Addison's and Graves's diseases, myxedema, cretinism, acromegaly, and others had alone received attention, while the influence of these organs on the diseases we meet in every day practice had been overlooked.

In keeping with all innovations which are thought to disturb orthodox knowledge, the newer interpretations submitted failed to gain support at first. Yet, seed was being sown and the plant finally began to bloom. This was expected to occur some time, even though tardily, because the mode of work pursued practically insured it. No one more than the author recognizes the commanding value of experimental demonstration; but if one grants such importance to *one* set of experiments, one must admit that many such experiments, *fifty* say, by different competent men working in kindred lines of research must prove fifty times more reliable, when co-ordinated, as a foundation for a sound conclusion. Particularly must this be the case when each experiment is analyzed and controlled through that great source of light, the clinical or practical field. This latter feature was especially available to the author, who, besides active practice and the constant drilling to which a teacher is subjected, had revised ten times the entire field of medicine for his *Annual of the Universal Medical Sciences* and its successor, the *Analytic Cyclopedia of Practical Medicine*, before he wrote *Internal Secretions*.

That human diseases are themselves superlatively instructive as sources of physiological data has been emphasized by a great physiologist, Professor Pawlow, who wrote in this connection: "The world of pathological phenomena is nothing but an endless series of the most different and unusual combinations of physiological occurrences which never make their appearance in the normal course of life . . . It is an interlinking of events the like of which," he adds, "could never enter into the mind of the present day physiologists." It was as a clinician, therefore, with the aid of all collateral data he could collect, including those afforded by physiology, besides personal laboratory work in anatomy, histology and biochemistry, and his current work as a practitioner, that the author reached the conclusions submitted.

In the present edition the author adduces evidence showing that physiologists have independently confirmed what seemed at one time almost heretical views, viz., conceptions of functions either differing totally from those generally taught in text-books of physiology, or which so far had remained wholly obscure. The far reaching meaning of these conceptions, precisely where practical medicine has failed to decrease mortality, may be illustrated by a few examples:—

The great function of pulmonary respiration, even as now taught in text-books and schools, had been found defective for over fifty years by several leading physiologists when the present work first appeared; but none had discerned the true process. The author pointed out that it was the secretion of the adrenals which took up the oxygen of the air in the lungs and thus caused hæmoglobin to be converted into oxyhæmoglobin. Physiological experiments by others fully confirmed this conclusion. Briefly, the adrenals proved to be the organs which, through their secretion, enabled the venous blood to be converted into arterial blood. Have we not in this the very soul of all functions, normal and pathological? Indeed, it became evident that the adrenals not only *sustained life* as fundamental organs of pulmonary respiration, general oxygenation and metabolism, but also that they took a direct part in the processes that *protect life.* Cellular oxygenation determining the activity of cellular function, and our defensive enzymes, antibodies, etc., being cellular products, do not fluctuations of the functional activity of the adrenals, which govern oxygenation, correspondingly influence defensive efficiency?

Such being the case, we should be able to govern our defensive functions, if, through our drugs, we could influence the activity of the adrenals. In the first edition, the author showed that several remedies produced their beneficial effects by stimulating these organs. One of our most familiar drugs, strychnine, for instance, was one of these. Recently, Stewart and Rogoff found experimentally that therapeutic doses of strychnine actually caused a marked and lasting increase in the production of the adrenal secretion. Do we not possess, in this action—and this applies to other familiar remedies—a fulcrum through which we can, at will, influence disorders of metabolism in which oxygenation is deficient? Its use in the convalescence of influenza and many other disorders clearly illustrates this fact.

Yet oxygenation represents but one phase of metabolism, *i.e.*, of cellular activity, through which our defensive resources are influenced. The thyroid apparatus was also shown, in the first edition, to take an active part in our defensive functions as a component of the systemic antitoxins or alexins, besides participating in the catabolic phase of general metabolism. This view has likewise been confirmed by various European experimenters. Here again, we find ourselves in the presence of a systemic opponent of disease quite within our pharmacological control.

Long has it been known that when all else fails in most chronic processes, the iodides will prove beneficial. Is not every one today familiar with the fact that it is by enhancing the functional activity of the thyroid apparatus, that iodine and the iodides produce their curative effects?

These few examples among the many that could be submitted, serve but to indicate the vast horizon that the first edition of the present work opened for the development of clinical medicine to the level of a science worthy of the name (the science that preventive medicine is growing to be) particularly in the field of therapeutics. If any one doubts the *need* of development in this direction, he has but to acquaint himself with the actual status of the one branch of clinical medicine through which the practitioner is expected to relieve suffering and cure the sick.

At the dawn of the present century, one of our foremost clinicians, Llewellys F. Barker, of Johns Hopkins, wrote that therapeutics was moribund; eight years later Sollmann, our foremost pharmacologist, wrote "at present it cannot be classed as an art nor as a science; it can only be classed as a confusion." Today therapeutics has been virtually eliminated from the curricula of practically all our larger medical schools.

What this means does not seem to have been apprehended by those upon whom rests the responsibility of deciding such questions. They overlook the fact that by allowing therapeutics to disappear from the list of subjects taught *they are insuring the doom of medicine itself.* Indeed, even empirical therapeutics, that of the day, is at least based on vast experience and observation, and affords material relief in suffering and often saves life. Virtually deprived of this knowledge by medical schools, graduates of the future will increasingly realize that their livelihood will no longer be earned honestly, unable as they will find themselves to meet the needs of those who, granting them unmerited confidence, will appeal to them for medical aid. Honorable men will increasingly abandon a career so little in keeping with their true aims, leaving the field open to the unscrupulous, the Christian Scientist and cults of all kinds. The phenomenal development of all such in recent years emphasizes already what the future has in store, if legitimate therapeutics is allowed to die.

It was with due reserve that nearly two decades ago the author submitted the opinion that it was because the internal secretions were overlooked in disease and therapeutics that the latter was losing its hold. He urged that the immense aggregate of pharmacological and clinical knowledge had not been accumulated in vain, and that therapeutics lacked *only*, when carefully co-ordinated and analyzed, the light that the internal secretions would cast upon it, to remove it definitely from the field of empiricism. Today, sustained by the authority of mature practical experience and analytical study of the whole field of medicine equaled in scope by no living man, the author has no hesitation in reiterating not only this assertion but what he likewise stated at the time, that it *was through the intermediary of the internal secretions, that most of our remedies, chemical and physical, produced their curative effects.*

It is not through organotherapy that therapeutics can be placed where it rightly belongs. Organic extracts in fact are but the shadows, often imperfect and sometimes inert, of the ductless glands they are supposed to represent. They are, however, serving a useful purpose in that they are affording at least an insight into the manner in which the endocrins influence disease either *morbidly* or *beneficially*. In conjunction with the diseases of the endocrins themselves, Graves's, Addison's, etc., organotherapy is only, as viewed by the author, one of the many sources of information capable under careful scrutiny, of furnishing materials—bricks and mortar—for the final elaboration of a medical edifice worthy of the name—a medicine from which guesswork and empiricism will forever be banished.

The initial efforts in the direction of this far reaching purpose were submitted in the first edition of the present work and developed in the succeeding editions. Steadily and increasingly, as previously stated, it is being found out that the author's conceptions can stand the test of time while pillars are being placed—unwittingly often—under the edifice he then tentatively erected.

The present or ninth edition, besides reviewing the present status of the physiology of all endocrins, the various diseases to which they are liable, and their rôle in the mental deficiencies of children, all as interpreted by the author, also takes up the subject of organotherapy. The one hundred pages devoted to this subject, however, portrays the experience of others, *i.e.*, of a large number of clinicians. All this experience, analyzed by the author, will enable the reader to grasp readily the *modus operandi* of the glands in many diseases, and prepare him for the contents of the second volume in which all processes concerned are fathomed more deeply.

The second volume, built upon the foundation started by the first, portrays the manner in which the endocrins elucidate our understanding of disease and therapeutics. The simpler principles of drug action are illustrated by the fifty most important remedies in use; while their application in practice, *with the endocrins as intermediaries* is explained with the aid of thirty-five of those of our major diseases which most clearly are influenced by the endocrins. Important in this connection is the fact that we are not dealing with a transformation of applied medicine. Indeed, knowledge of the endocrins as interpreted by the author, ***does not impose upon the trained physician the necessity of unlearning what he has acquired through hard study and practical experience;*** it ***adds*** to that knowledge and enhances his efficiency.

The ninth edition also introduces a new feature in this connection. The author, during the years he has studied endocrinology has found the introduction of the endocrins in the consideration of disease particularly helpful in certain disorders. These are reviewed succinctly in a supplement at the end of the second volume. The list includes some diseases which, in so far as mortality is concerned, have no peer: influenza, arteriosclerosis and senile pneumonia, for instance—all interpreted and treated on newer lines. Diseases of the mind, dementia precox in particular, which sends thirty thousand of our children to asylums each year, are also shown in many instances to depend, in part, upon functional disorders of the endocrin glands and to be influenced favorably by remedies or measures which influence these organs.

The author, in fact, does not hesitate to attribute to the absence of the endocrins in the pathology of most mental diseases much of the unfavorable therapeutic results that psychiatrists, notwithstanding most faithful and far reaching efforts, have encountered. And this may be said to apply to practically all diseases met in every-day work which have so far defeated our efforts.

In closing, the author wishes again to urge that knowledge of the functions of the internal secretions and of their influence in practice, in so far as pathogenesis, diagnosis, and therapeutics are concerned, may be regarded as the most constructive asset ever bestowed upon internal medicine by the thousands of clinicians and investigators who have given it the benefit of their endeavors. Endocrinology sacrifices nothing of what we actually know; it adds to, and elucidates all we know, and, on the whole, it appeals to our highest aims, the relief of human suffering.

CHARLES E. DE M. SAJOUS.

Philadelphia, Sept., 1920,

TABLE OF CONTENTS OF VOLUME FIRST.

CHAPTER I.

PAGE

- SIGNIFICANCE OF THE INTERNAL SECRETIONS IN THE PRACTICE OF MEDICINE 1
  - THE ADRENALS IN THEIR RELATION TO DISEASE AND TREATMENT 2
    - Heart Disease 8
      - Chloroform Anesthesia 8
      - Heart Failure 9
      - Senile Heart 9
      - The Arrhythmias 11
        - in Acute Infections 11
        - in Irritable Heart 11
        - in Neuro-cardiac Asthenia 11
        - in Adolescence 11
      - Auricular Fibrillation 12
      - Auricular Flutter 12
      - Heart Block 12
      - Sinus Arrhythmia 12
    - Pulmonary Disorders 12
      - Senile Pneumonia 14
      - Bronchial Asthma 14
    - Renal Disorders 15
      - Acute Nephritis 15
      - Chronic Nephritis 15
      - Ascites 17
      - Serous Effusions 17
    - General Infections 18
      - Asiatic Cholera 18
      - Choleraic Diarrhœa 18
      - Typhoid Fever 18
      - Pneumonia 19
      - Bronchopneumonia 19
      - Influenza 19
      - Pernicious Malaria 19
      - Scarlatina 19
      - Measles 19
      - Septicemia 19
      - Anthrax 19
      - Gaseous Gangrene 19
      - Adrenal Apoplexy 19
  - THE THYROID GLAND IN ITS RELATIONS TO DISEASE AND TREATMENT 20
      - Hypothyroidia 23
      - Migraine 24
      - Urticaria 24
      - Eczema 24
      - Enuresis 24
      - Catarrhal Disorders 24
      - Alopecia 24
      - Metrorrhagia 25
      - Leucorrhœa 25
      - Abortion 25

PAGE
Rheumatic Disorders 25
Rheumatism 26
Arthritis Deformans 26
Pulmonary Disorders 27
Pulmonary Tuberculosis 27
THE PANCREAS IN DISEASE AND TREATMENT 30
Cardiac and Valvular Disorders 33
Endocarditis 35
Pleurisy 35
Pericarditis 35
Peritonitis 35
METABOLIC DISORDERS 35
Glycosuria 35
Diabetes Mellitus 35
Diabetes Insipidus 40
Hepatic Disorders 41
Portal Cirrhosis 41
Acute Yellow Atrophy 43
Amyloid Liver 43

CHAPTER II.

THE FUNCTIONS AND DISEASES OF THE ADRENALS 45
Structure of the Adrenals and the Chromaffin System 45
Histology of the Adrenals 48
The Medulla 48
The Cortex 50
The Blood-supply 53
The Lymphatics 54
The Nerve-supply 54
Subsidiary Adrenal and Interrenal Tissues 55
The Carotid Glands 55
The Coccygeal Body 56
The Tympanic Glands 56
The Organ of Zuckerkandl 56
The Subsidiary Interrenal Tissues or Adrenal Rests 57
The Adrenal Secretion in Respiration and Metabolism 59
The Adrenal Secretion in Pulmonary Respiration 60
The Governing Center of the Adrenals 71
Hypoadrenia 80
Various forms of 82
Functional Hypoadrenia 82
Functional Hypoadrenia of Infancy and Childhood 83
Functional Hypoadrenia in the Adult 85
Functional Hypoadrenia of Old Age 88
Prophylaxis and Treatment 89
Addison's Disease, or Chronic Progressive Hypoadrenia 97
Pathogenesis and Symptomatology 99
Treatment 103
Terminal Hypoadrenia 109
Pathogenesis and Symptomatology 110
Pathology 111
Treatment 112
Hyperadrenia 115
Acute Hyperadrenia and Adrenal Hæmorrhage 116
Pathogenesis and Symptomatology 118
Adrenal Hæmorrhage in the Newborn 118

PAGE
Adrenal Hæmorrhage in Children 120
Adrenal Hæmorrhage in Adult 121
  Diagnosis 123
  Prognosis 124
  Treatment 124
Adrenal Hæmatoma 126
  Pathogenesis and Symptomatology 126
  Diagnosis 128
  Prognosis 129
  Treatment 129
Hypernephroma 129
  Pathogenesis and Symptomatology 130
Malignant Hypernephroma of the Adrenals 131
  Diagnosis 132
Hypernephroma of the Kidney 132
  Diagnosis 134
  Pathology 136
  Prognosis 137
  Treatment 137
Cancer of the Adrenals 137
  Varieties 137
  Symptoms 138
  Diagnosis 140
  Treatment 141

CHAPTER III.

THE THYROPARATHYROID APPARATUS IN GENERAL OXIDATION AND IMMUNITY 143
  Prevailing Views as to the Functions of the Thyroid and Parathyroids 143
  Removal of the Thyroid Only 144
  Removal of the Parathyroids Only 146
  Dual Function Theory 147
  Effects of the Internal Secretion of the Thyroid 148
  Effects of the Internal Secretion of the Parathyroids 149
  Obscure Features of the Thyroparathyroid Problem 150
  The Thyroparathyroid Secretion as an Oxidation Activator through its Action on Cellular Phosphorus 152
  The Thyroparathyroid Secretion as Wright's Opsonin 163
  The Pituitary Body as the Seat of Thyroparathyroid Center 168

CHAPTER IV.

DISEASES OF THE THYROPARATHYROID APPARATUS 174
  Disorders due to Deficient Activity of the Thyroparathyroid Apparatus 174
  Hypothyroidia 175
    Etiology and Pathology 183
    Treatment 184
  Myxœdema, or Progressive Hypothyroidia 185
    Symptomatology and Pathogenesis 186
    Etiology 191
    Pathology 191
    Treatment 192
  Infantile Myxœdema, or Cretinism 193
    Symptomatology and Pathogenesis 193

PAGE

  - Etiology 196
  - Pathology 198
  - Treatment 198
- Myxœdematous Infantilism 201
  - Symptomatology and Pathogenesis 201
  - Diagnosis 204
- Lorain Type of Infantilism 204
- Mongolian Infantilism 205
- Achondroplasia, or Fœtal Rickets 205
  - Treatment 206
- Thyroid Hyperæmia and Thyroiditis 206
  - Symptomatology 207
  - Diagnosis 209
  - Treatment 209

CHAPTER V.

DISEASES OF THYROPARATHYROID APPARATUS (*Continued*) 212

- Disorders due to Excessive Activity of the Thyroparathyroid Apparatus 212
- Hyperthyroidia 212
- Exophthalmic Goiter 214
  - Pathogenesis and Symptomatology 216
    - Sthenic or First Stage 217
    - Transition Stage 222
    - Asthenic or Myxœdematous Stage 222
  - Enlarged Thymus as Complicating Factor 223
    - Etiology 227
    - Treatment 232
  - Surgical Treatment 238
    - Indications 238
    - Operative Risks and Results 241
- Goiter 243
  - Etiology 244
  - Varieties 247
  - Simple Hypothyroid Non-toxic Goiter 249
    - Pathology 251
    - Prognosis 251
    - Treatment 251
  - Hyperthyroid or Toxic Goiter 258
    - Treatment 258
  - Hypothyroid Degenerative Goiter 259
    - Colloid Goiter 260
    - Cystic Goiter 261
    - Fibrous Goiter 261
    - Intrathoracic Goiter 261
    - Constrictive Goiter 262
    - Lingual Goiter 262
    - Hæmorrhagic Goiter 262
  - Symptoms of Degenerative Goiter 263
  - Treatment 265
  - Surgical Treatment 266
    - Operative Risks and Results 269
- Malignant Goiter 270
- Congenital Goiter, or Goiter in the Newborn 272
  - Symptoms 272
  - Treatment 273

PAGE
- Strumitis, or Inflammation of a Goiter 274
  - Symptoms 274
  - Prognosis 275
  - Treatment 275

CHAPTER VI.

THE THYROID, THYMUS, PITUITARY, AND ADRENALS IN MENTAL DEFICIENCY 277
- Idiocy and Mental Backwardness in Children 277
- The Thyroid Apparatus in Mental Deficiency 278
  - Stigmata of Deficient Thyroid Activity 278
- The Functions of the Thymus 280
  - Stigmata of Deficient Activity of the Thymus 288
- Mongolian Idiocy 289
  - Etiology and Pathogenesis 292
  - Pathology 294
  - Treatment 295
- The Adrenals in Idiocy 297
  - Stigmata of Deficient Activity of the Adrenals as a Whole 300
  - Stigmata of Deficient Activity of the Adrenal Cortex 300
  - Stigmata of Excessive Activity of the Adrenal Cortex 301
- Amaurotic Family Idiocy 303
  - Treatment 306
- Dystrophia Adiposo-genitalis 307
  - Treatment 309
- The Backward Child 309
  - Diagnosis and Pathogenesis 310
  - Treatment 311
- The Prophylaxis of Mental Deficiency in Children 314
  - Prophylactic Treatment 318
  - Development of the Senses 322
    - Hearing 322
    - Vision 323
    - Smell and Taste 323
    - Cutaneous Sensibility 324

CHAPTER VII.

DISORDERS DUE TO DYSFUNCTION OF THE INTERNAL SECRETIONS 325
- Dementia Præcox 325
- Pathological Effects of Overactive Internal Secretions 342
  - Valvular Disease 345
  - Acute Myocarditis 345
  - Pleurisy 346
- Disorders of the Liver 346
  - Alcoholic Cirrhosis 347
  - Acute Yellow Atrophy 347
- Disorders of the Pancreas 348
  - Acute Pancreatitis 348
- Disorders of the Intestine 349
  - Typhoid Fever 349
- Disorders of the Nervous System 349
  - Acute Myelitis 350
  - Tabes Dorsalis 350
- Failure of the Adrenals as Cause of Disease 352

PAGE
Influenza 352
Adrenal Apoplexy 356

CHAPTER VIII.

THE ADRENAL SECRETION AND FUNCTIONAL ACTIVITY 357
The Internal Secretions of the Pancreas and Spleen 359
Glycosuria and Overactivity of the Adrenal System 362
The Functional Relationship between the Pancreas and Spleen . 367
The Functional Mechanism of the Pancreas 381
The Functional Mechanism of the Spleen 385
The Spleno-pancreatic Internal Secretion 392

CHAPTER IX.

THE ADRENAL SECRETION IN THE FUNCTIONS OF THE HEART AND LUNGS 421
The Adrenal Secretion as the Source of the Functional Activity of the Right Heart 421
The Action of the Adrenal Secretion and the Oxidizing Substance upon the Cardiac Muscle 433
The Innervation of the Heart 444
Acceleration 445
Inhibition 446
Augmentation 449
The Adrenal Secretion in its Relation to Respiratory Functions 453
The Nervo-vascular Mechanism of the Lungs 454
The Adrenal System and the Kidneys 467
The Adrenal System and the Generative Glands 473
Testicles 473
Ovaries 478

CHAPTER X.

THE POSTERIOR PITUITARY AS A GENERAL NERVE-CENTER AND AS CO-CENTER OF THE ANTERIOR PITUITARY IN SUSTAINING LIFE 483
The Identity of the Lower Brain 483
Histology of the Posterior Pituitary Body 493
Clinical Evidence 511
The Histology and Physiological Chemistry of the Neuron 518
The Physiological Chemistry of Nerves 532
The Circulation of the Neuron 539
The Physiological Chemistry of the Neuron 552
The Minute Circulation of the Cerebro-spinal Substance 562
The Posterior Pituitary Body as the Somatic Center of the Nervous System 591
The Posterior Pituitary as the Sensorium Commune 598
Efferent (Motor) Impulses 601
Afferent (Sensory) Impulses 603
Acromegaly: Pierre Marie's Disease, and Gigantism 607
Pathogenesis and Symptomatology 608
Sthenic Stage 610
Asthenic Stage 613
Pathology 616
Treatment 618

CHAPTER XI.

PAGE
THE INTERNAL SECRETIONS AND THE LEUCOCYTES IN IMMUNITY AND FEVER 620
The Adrenal System as the Foundation of Immunity 620
Adrenals 622
Thyroparathyroid Apparatus 623
The Pituitary Body as the Seat of the Immunizing Center .. 624
The Mode of Action of the Immunizing Mechanism and the Genesis of Fever 628
Concluding Remarks 632
The Leucocyte in its Relations to Nutrition, Organic Functions, and Immunity 633
The Mitoma 633
Functional Mechanism of the Leucocyte 639
The Granules as Secretory Products 644
The Physiological Chemistry of Leucocytes 647
Classification of Leucocytes 650
Lymphocytes and Hyaline Cells 652
Neutrophile Leucocytes 653
The Neutrophile Leucocytes in Assimilation 654
Ehrlich's Eosinophile Leucocytes 667
The Basophile Leucocytes 680
The Functions of the Leucocytes in Immunity 691
How Bacterins (Vaccines) Act and How Opsonins Enhance Phagocytosis 696
A Simplified Theory of Immunity 698

CHAPTER XII.

THE INTERNAL SECRETIONS AND ORGANOTHERAPY 700
The Fundamental Principles of the Action of Organic Preparations 700
Thyroid Organotherapy 708
Insanity 711
Epilepsy 716
Obesity 724
Adiposis Dolorosa; Dercum's Disease 727
Goiter 728
Chronic Rheumatism 729
Enuresis 733
Skin Diseases 734
Hæmophilia 736
Surgical Disorders 737
Febrile Infections 738
Cancer 739
Parathyroid Organotherapy 739
Hypoparathyroid Tetany 741
Symptomatology 742
Post-operative Parathyroid Tetany 742
Non-operative Hypoparathyroid Tetany 743
Treatment 744
Paralysis Agitans 747
Adrenal Opotherapy 750
Surgical Diseases 752
Shock and Collapse 754
Hæmorrhage 755

PAGE

  - Toxæmias 756
  - Cancer 757
  - Cardiac Disorders 758
  - Respiratory Disorders 761
  - Ascites and Other Effusions 762
  - General Indications of Adrenal Preparations 764
- Pituitary Organotherapy 765
  - Cardiac Disorders 767
  - Obstetrics 768
  - Infectious Diseases 770
  - Acromegaly 771
  - Exophthalmic Goiter 772
  - Nervous and Mental Diseases and Myopathies 773
  - Stunted Growth and Imbecility 773
  - Intestinal Paresis 774
  - Arthritis 775
  - Rachitis 775
  - Asthma 775
  - Hemoptysis 776
- Ovarian Organotherapy 776
  - Natural and Artificial Menopause 777
- Corpus Luteum Organotherapy 779
  - Menstrual Disorders; Menopause; Oöphorectomy 779
  - Sterility; Infantile Generative Organs; Habitual Abortion; Hyperemesis of Pregnancy 780
- Orchitic or Testicular Organotherapy 781
  - Tabes 782
  - Neurasthenia 782
  - Melancholia 782
  - Impotence 782
  - Paralysis Agitans 782
  - Eczema 782
  - Psoriasis 782
  - Gout 782
  - Obesity 782
  - Glycosuria 782
  - Acne 782
  - Rheumatism 782
  - Syphilis 782
  - Marasmus 782
  - Typhoid Fever 782
  - Diphtheria 782
  - Cholera 782
  - Addison's Disease 782
- Kidney Organotherapy 782
  - Epilepsy 783
  - Chronic Nephritis 784
  - Bright's Disease 784
  - Puerperal Intoxications 784
- Mammary Gland Organotherapy 785
  - Uterine Fibroid 785
  - Uterine Subinvolution 785
  - Lactation 786
- Thymus Organotherapy 786
  - Diseases of Thyroid 786
    - Goiter 786
    - Exophthalmic Goiter 786

PAGE
Rachitis, or Rickets 787
Brain and Nerve Substance Organotherapy 788
  Tetanus 788
  Hydrophobia 788
  Strychnine Poisoning 788
  Morphine Poisoning 788
  Neurasthenia 788
  Hysteria 788
  Chorea 788
  Tic 788
  Epilepsy 788
The Pineal Gland Organotherapy 789
  Backward Children 789
Hormone Therapy 789
  Chronic Constipation 790
  Post-operative Intestinal Paralysis 790
Pluriglandular Therapy (considered in Vol. ii, p. 1825) 790

INDEX TO VOLUME FIRST 791

ILLUSTRATIONS IN VOLUME FIRST.

PAGE
he Adrenal System (*Sajous*) .... Frontispiece
irculation of the Adrenals in the Dog (*J. M. Flint*) 46
he Adrenal Vessels in the Young and Old (*Landau*) 88
ypothyroidia (*Léopold-Léri and de Rothschild*) 182
hyroid Extract in Cretinism (*McGee*) 200
ascular Supply of the Thyroid Gland (*Pochet-Johnson*) 218
nencephaly (*McKee and Wells*) 297
amera-Lucida Tracing of the Lobule Boundaries in One of a Series of Sections from the Splenic End of a Cat's Pancreas (*Eugene L. Opie*) 398
ermination of Small Blood-vessels in the Spleen (*Gray*) 401
irculation of the Human Heart (*Arthur V. Meigs*) 436
echanism of Cardiac Action (*Sajous*) 444
enile Transformation of Clitoris and Adult Hirsuties due to Hypernephroma in Girl of Seven Years (*Jump, Beates, and Babcock*) 476
edian and Vertical Section of a Three Months' Embryo (*Dejerine*) 490
ertical Section of the Posterior Pituitary body (*Berkley*) 494
arious Types of Cells in the Posterior Pituitary Body (*Berkley*) 496
arious Types of Cells in the Posterior Pituitary Body. Portion of Glandular Elements of the Anterior Pituitary Body (*Berkley*) 498
Median and Vertical Section of a Two and One-half Months' Embryo (*His*) 510
Diagram of Relation between Longitudinal and Transverse Sections showing Cones Cut Across at Different Levels (*W. H. Wynn*) 537
Nerve-fibers from a Frog Injected with Methylene-blue (*Kölliker*) 541
Sensory Nerve-ending Stained with Methylene-blue in the Exocardium of the Left Auricle of a Gray Rat (*Smirnow*) 542
Lesions in the Neurons of Animals after Ricin Poisoning (*Berkley*) 550
Lesions in the Neurons of Animals after Ricin Poisoning (*Berkley*) 552
Schematic Representation of the Lower Motor Neuron (*Barker*) 558
A Protoplasmic Glia-cell from a Human Brain (First Layer of Cortex) (*Andriezen*) 564
Leucocytes in the Perivascular Spaces and in Vessels, as a Result of Acute Alcoholic Poisoning (*Berkley*) 572
A Protoplasmic Neuroglia-cell from the Human Brain (Fourth Layer of Cortex), showing Two Expanded Conical Disk-like Attachments to a Vessel (*Andriezen*) 584

PAGE

Relationship of the Vascular and Lymph Channels in the Brain (*Andriezen*) 586

Blood-vessel of the Human Brain, showing Several Neuroglia Fiber-cells Surrounding it and Forming a Felt-work (Perivascular System) (*Andriezen*) 587

Seven Caudate Fiber-cells from the Human Brain-cortex (First Layer) (*Andriezen*) 589

Terminal Tufts and Endings of the Protoplasmic Apical Processes in the First Layer (Human Brain-cortex) (*Andriezen*) 590

Semidiagrammatic Transverse Vertical Section of the Infundibular Region of the Brain (*Berkley*) 594

The Posterior Pituitary Body as General Center of the Nervous System (*Sajous*) 598

Case of Acromegaly, Exophthalmic Goiter, Phthisis, and Glycosuria (*Murray*) 610

Pituitary Body, Containing Immunizing Center (semischematic) 627

Leucocytes; their Mitoma and Microsomes (*Gulland*) 634

Intraphagocytic Destruction of Bacteria (*Metchnikoff*) 692

Cretinic Obesity (*Sanderson*) 724

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CHAPTER I.

SIGNIFICANCE OF THE INTERNAL SECRETIONS IN THE PRACTICE OF MEDICINE.

THE present work differs from all others on endocrinology published so far, in that its aim is to show that the ductless glands fulfill as important a rôle in disease and therapeutics as is now attributed to any of the more familiar organs of the body, the liver, the lungs, the kidneys, etc. Hence its title "The Internal Secretions and the Principles of Medicine." When, therefore, Swale Vincent[1] wrote: "Sajous apparently postulates a relationship between all the ductless glands whose functions, according to this writer, dominate most of the bodily activities, normal and pathological", referring to the first edition of this work published in January, 1903, he faithfully portrayed the broad functional rôle 1 attributed to these organs. The progressive development of such a connection throughout the whole realm of medical thought indicates that time has sanctioned the position then taken.

The purpose of the present chapter, is to illustrate, as a preamble, by means of many notable examples, that those diseases most costly in human lives are profoundly influenced and even caused in many instances by the endocrins; but also that through their intermediary, our therapeutic efficiency may be greatly enhanced.

It must frankly be said, however, that to portray the significance of endocrine factors in internal medicine with only the prevailing conceptions of the functions of any ductless gland as basis is an impossibility. While sound as far as they go, they do not supply the needs of so far reaching a connection. Experimental work has always needed the crucial test of the practical field to gain lasting recognition, each experimental deduction being tested out as it were, in disease after disease to ascertain whether it fulfills a *bona fide* rôle in its physio-pathology and really means what it purports to represent. Such analytical work, in itself, however, is a prolific source of information, and it was in doing it over two decades ago, and testing each thought in collateral fields besides, that I reached conclusions (1903-1907) in respect to certain endocrines which I deem fundamental and absolutely necessary to even approximately fulfill a task such as that described in the heading of this section. Four of these fundamental functions have so far stood the test of time in that both the clinic and the laboratory have indicated their soundness. These are: 1, That the adrenal secretion endows the hæmoglobin molecule with its power to become converted into oxyhæmoglobin in the pulmonary alveoli and to carry on general oxygenation; 2, that the thyroid secretion takes part in the immune chemistry of the body as opsonin and indirectly the production of antitoxins through its participation in metabolism; 3, that trypsin is an active factor in cellular metabolism and immune chemistry; and 4, that the pituitary body—irrespective of any secretory function it may possess—is connected by nerve paths with the adrenals through which it influences the secretory activity of the latter. Although the evidence submitted is but a fraction of that available in the body of the work, it was deemed sufficient to indicate the strength of data supporting the personal conclusions submitted in respect to disease.

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[1] **Swale Vincent: Internal Secretions and the Ductless Glands. London, 346, 1913.**

Pending more elaborate studies, submitted farther on in these volumes, what endocrine functions are needed in the present connection will be briefly summarized to illustrate the part they take in morbid processes and their treatment.

THE ADRENALS IN THEIR RELATION TO DISEASE AND TREATMENT.

The prevailing theories concerning the physiological functions of the adrenals were summarized in 1919 by Lewellys F. Barker[2] as follows: "1. The *tonus* theory, which assumes that epinephrin maintains in some way constantly a state of tonus in smooth muscle innervated by the sympathetic nervous system. 2. The *emergency* theory which regards the suprarenals as an apparatus for discharging epinephrin in emergencies only. 3. The *antitoxic* theory, according to which the suprarenal secretion neutralizes poisons, or its variation which assumes that the suprarenal products themselves are detoxicated substances. 4. The *metabolic* theory, which postulates that the presence of minute quantities of epinephrin are necessary for the metabolic activities of the tissues, including oxygenation of the blood." Which of these postulates actually represents the true function of the adrenals?

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[2] Lewellys F. Barker: Endocrinology, iii. 253, 1919.

Studied from the comprehensive viewpoint referred to above, *all* the postulates enumerated by Barker (excepting perhaps the theory that the adrenal products are detoxicated substances) have held their own. In order to understand their connection with disease, however, emphasis must be laid upon that part of the metabolic theory summarized in the five last words "including oxygenation of the blood," which happens to be my own contribution to the function, a *fundamental* one as we shall see.

The respiratory process as now taught, is by no means accepted by all physiologists. Ever since the middle of the last century the diffusion doctrine of pulmonary respiration had been found incompatible with many experimental facts. Such authorities as Robin, Verdeil, Garnier, Duval, in France, Haldane and Lorrain Smith, in England, and notably Bohr, of Denmark,[3] found that the normal oxygen tension in arterial blood was often higher than the alveolar air. The Anglo-American Expedition to Pike's Peak in 1911 also observed that often at this high altitude, the oxygen tension in the blood became considerably higher than that in the alveolar air. While Haldane and the Oxford school explained this phenomenon by attributing to the lungs the power to clutch the oxygen and, through the alveolar epithelium force it into the blood, Bohr and Henriques[4] held that the process required a substance "having greater avidity for oxygen than the blood itself," . . . . "a kind of internal secretion." The nature of this internal secretion, however, they failed to determine.

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[3] C. Bohr: Archiv f. Physiol., ii, 236, 1891.

[4] Bohr and Henriques: Arch. de Physiol., ix, 459, 1897.

In 1900, various chemical, anatomical, physiological, biological and clinical facts, to be reviewed later in these pages, suggested that the adrenal product might be the "internal secretion" sought by Bohr to meet the needs of the respiratory process. A comprehensive study of each phase of the subject led me (1903)[5] to the conclusion: 1, That "the relative tension of oxygen in the blood and in the alveolar air is not a ruling factor in the process of respiration"; 2, that the secretion of the adrenals "which leaves these organs through the suprarenal veins, is mixed with the plasma of the venous blood in the inferior vena cava"; 3, that "when the venous blood reaches the pulmonary alveoli, the marked affinity of the adrenalized plasma for oxygen causes it to absorb this gas from the alveolar air"; 4, that "the red corpuscles, after this operation, bathe in an oxygen-laden medium, and their hæmoglobin becomes reconverted into oxyhæmoglobin."

This interpretation has been confirmed both directly and indirectly. Adrenin (the adrenal secretion or juice) was found to increase the intake of oxygen and the output of carbon dioxide by Byelaventz.[6] Bernstein and Falta[7] obtained similar results from 1 milligramme of adrenalin subcutaneously in normal subjects, and Tompkins, Sturgis and Wearn[8] from intramuscular injections of 8 minims of the 1:1000 solution of adrenalin. The latter observers also noted that the respiratory rate was augmented, while D. E. Jackson[9] found that it produced prompt dilatation of bronchioles when these were contracted. Nice, Rock and Courtright[10] observed that both minute and large doses of adrenalin evoked an increase in the depth of respiration, while Sandiford[11] found that it caused an increase of heat production of the respiratory quotient of the ventilation rate and of the respiration rate Biology also contributes confirmatory evidence. H. H. Dale,[12] for instance, recalls that Abel "had found adrenin in relatively enormous quantity in the skin glands of the toad, where," he remarks, "it would seem to serve no possible function and might easily be regarded as a waste product." With the adrenal secretion as an active participant in the respiratory process, the presence of adrenin in the skin of these batrachians meets a self-evident need in view of the familiar fact that the skin forms part of their respiratory apparatus.

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[5] C. E. de M. Sajous: Internal Secretions and the Principles of Medicine, Phila., i, 127, 1903.

[6] P. P. Byelaventz: Rousskii Vratch, ii. 247, 1903.

[7] Bernstein and Falta: Verhandl. d. deut. Kongr. f. inn. Med., xxxix, 536, 1912.

[8] Tompkins, Sturgis and Wearn: Arch. Internal Med., xxiv, 269, 1919.

[9] D. E. Jackson: Jour. Pharm. and Exper. Therap., iv, 291, 1913.

[10] Nice, Rock and Courtright: Amer. Jour. Physiol., xxxiv, 326, 1914.

[11] I. Sandiford: Ames. Jour. Physiol., ii. 407, 1920.

[12] H. H. Dale: Proc. Royal Soc. of Med.; Therap. and Pharm. Sect., London, vii (3), 34, 1913-1914.

As regards the personal conclusion that the adrenal secretion enables the hæmoglobin to become converted into oxyhæmoglobin on exposure to the alveolar air, Kariya and Tanaka,[13] in 1913, found that adrenalin could itself act as does hemoglobin. Menten and Crile[14] then also found experimentally that blood from the adrenal vein—which transfers the adrenal secretion to the vena cava—invariably assumed a bright red arterial color in from one to twenty minutes after dilution with salt solution, while blood from other organs treated in the same manner, showed no change. Again, having added adrenalin to diluted human venous blood, Menten[15] found that it caused an increase in the intensity of the oxyhæmoglobin absorption-bands, stating that she regards this as "unquestionably very strong evidence that it is adrenalin which is responsible for the increased amount of oxyhæmoglobin found in the adrenal vein blood."*

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[13] Kariya and Tanaka: Jour. Tokyo Med. Assoc., xxvi, No. 20, 1913; Abst. in Sei-I-Kwai Med. Jour., xxxii, 10, 1913.

[14] Menten and Crile: Cited by Menten: Amer. Jour. Physiol., xliv, 176, 1917.

[15] M. L. Menten: *Ibid.*

* As collateral evidence, it may also be stated that the third personal conclusion submitted, *i.e.*, that "on reaching the alveoli the marked affinity of the adrenal substance causes it to absorb this gas from the alveolar air," is sustained by the theory of Haldane and the Oxford school, that when the oxygen tension in the alveolar air is low, the alveolar epithelium can seize the oxygen and force it into the blood to compensate for the deficiency of that gas. From my viewpoint it is the powerful reducing power of the adrenin in the venous blood which enables it to absorb oxygen forcibly through the alveolar epithelium, and thus to raise the arterial oxygen tension. This is well shown by the experiment of Müller which showed that a strangulated animal exhausted *all* the oxygen in its alveolar air.

The contention of Haldane and the Oxford school has been opposed by Barcroft[16] and the Cambridge school after the former had spent six days "in a glass respiration chamber in which the partial pressure of oxygen was reduced until it was its lowest—about 45 millimeters." He states that his blood had *become dark*, and that "the most careful analysis failed to discover any evidence that the body can force oxygen into the blood in order to compensate for a deficiency of that gas in the air." From my viewpoint and judging from the suffering endured by Prof. Barcroft, his blood was nearly anoxic, due to the fact that his tissues were reducing his oxyhemoglobin *more rapidly* than the excessively low partial pressure of oxygen in his alveolar air could satisfy. The result was that notwithstanding an ample supply of adrenin in his venous blood, it could not reduce sufficiently the alveolar air to enable it to convert his hemoglobin into oxyhemoglobin and his blood remained venous, *i.e.*, "dark." This in no way, however, militates against Haldane's view, when the cardinal rôle of adrenin in the process is taken into account.

[16] J. Barcroft: Jour. of Physiol., liii, 450, 1919-1920.

Barker's fourth conclusion attributes so predominating a function as metabolism to "the presence of minute quantities of adrenalin." This statement is doubtless based upon the older estimates of Trendelenburg,[17] Battelli,[18] Barger,[19] and others. Biedl, however, found that about 4.3 milligrammes was secreted into the blood every twenty-four hours—a large quantity, even from the pharmacological standpoint, particularly in view of A. E. Schäfer's observation that fourteen millionths of a gramme of the adrenal principle per kilo of animal sufficed to produce maximal effects. As to the production of the adrenal secretion itself, adrenin, Stewart and Rogoff[20] in a study of the spontaneous liberation of this secretion in the cat, found that it varied from 0.0003 to 0.001 gramme a minute per kilo of animal, At this rate, a man weighing 70 kilos would receive in his blood 1.26 to 4.20 cubic centimeters of adrenin per hour, *i.e.,* over 30 to 100 cubic centimeters in the twenty-four hours, ample to meet the needs of oxygenation and metabolism. Moreover, there is good ground for the belief that several bodies now identified under other names in the blood and other fluids, the liver, intestines, feces and urine, are more or less rich in adrenin.

Clinical observation confirms the teaching of physiological experimentation that while excessive activity of the adrenals raises temperature, deficient activity lowers it. Thus, Lépine,[21] Morel[22] and many other clinicians have noted that even non-toxic doses of adrenal extracts raised the temperature from 0.5 to 1° C. (0.9 to 1.8° F.). Tumors of the adrenals, particularly those of the true malignant hypernephroma type, are also known to follow a febrile course; even malignant tumors in general cause elevation of temperature in 57 per cent. "wholly independent of any fever producing complications," when the adrenals are involved, according to Israel,[23] while the same tumors in the kidney alone cause a rise of temperature in but 2 per cent. of the cases. Courmont[24] also observed that large adrenal grafts produced "a formidable hyperthermia" and "disastrous results" in the absence of all infection—a phenomenon likewise noted by other operators. The premature development in the malignant hypernephroma of childhood, so marked in some instances that the child appears, as to size and development, twice or three times its true age, bespeaks the activity of the cellular oxidations sustained by these adrenal neoplasms. Conversely, the Addisonian syndrome which includes hypothermia, with low oxygen intake and carbon dioxide output, marked asthenia, low blood-pressure, small and feeble pulse, etc., all of which correspond with the results of adrenalectomy, fittingly represent the effect of functional insufficiency of these glands on general oxygenation.

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[17] Trendelenburg: Cited by R. G. Hoskins: Endocrinology, i, 151, 1917.
[18] M. F. Battelli: C. r. de la Soc. de Biol., Paris, liv, 1179, 1182, 1902.
[19] G. Barger: Monograph on Biochemistry, London, 98, 1914.
[20] Stewart and Rogoff: Jour. Pharm. and Exper. Therap., viii, 479, 1916
[21] R. Lépine: La Semaine Méd., xxiii, 53, 1903.
[22] L. E. Morel: Le Progrès Méd., xxxii, 63, 81, 1903.
[23] J. Israel: Deut. med. Woch., xxxi, 1745, 1905.
[24] Paul Courmont: Titres et Trauvaux Scientifiques, Lyon, 90, 1907.

The bearing of this causal relationship between the adrenal secretion and the processes of pulmonary and tissue oxygenation, upon the other postulates enumerated by Barker will now suggest itself.

As regards the *tonus theory* introduced by Oliver and Schäfer in 1894, fluctuations of oxygenation and, therefore, of metabolic activity, in the myoneural junctions of tissues such as the smooth muscles, innervated by the sympathetic system (known to be especially rich in chromaffin or medullary adrenal substance) account for any variation of contractility that quantitative modifications in the supply of adrenin may provoke. This is a feature of exceeding importance in disease, we shall see, particularly in its bearing upon the arterioles and the heart. Cannon's *emergency theory,* in which the functions of the adrenals are roused during emotional stress, fear, anger, pain, asphyxia, etc., also finds its explanation since the excitement, preparation for defense, flight, attack, etc., necessitates a correspondingly marked increase in the rate of metabolism, respiration and oxygenation.

Whether as Cannon thinks, there is little or no adrenin secreted between periods of stress, might apply as well to the metabolic theory, adrenin being produced only to meet the needs of the hæmoglobin—a possibility favored by the fact that as an oxidizing enzyme (which I have termed adrenoxidase), the adrenal principle may carry on its functions without being itself destroyed. The *antitoxic theory* of Abelous and Langlois, originally limited to the destruction of fatigue or muscular wastes, also finds its explanation. If we realize that all functions, including those of bodily defense, the formation of antibodies, phagocytes, etc., depend upon metabolic activity and tissue oxygenation, the manner in which an exacerbation of secretory activity of the adrenals or the therapeutic use of its principle may enhance the antitoxic efficiency suggests itself. As to the *metabolic theory*, it is perhaps unnecessary to repeat that, as is the case with the three others, oxygenation is the essential or fundamental feature of the process itself.

To illustrate the bearing of these deductions upon disease and treatment, the morbid processes with which so far the adrenals have shown an unmistakable connection will be briefly reviewed.

HEART DISEASE.—Modern studies have increasingly emphasized the importance of the heart muscle in cardiopathies, particularly the nature and source of the agencies which sustain its functional efficiency and the rhythm of its contractions. And yet, probably the most important of these agencies, the adrenal secretion, has been overlooked to such a degree that even the most modern works on cardiology fail to refer to it in this connection, although the ubiquitous use of adrenalin in the heart failure of acute infections and many other clinical facts have fully sustained the teachings of Oliver and Schäfer that adrenin sustains the tonus of smooth muscle, to which class the heart muscle belongs. Again, its participation in cardiac function is further emphasized by the familiar fact that smooth muscle is innervated by the sympathetic,[*] and that one of the essential functional constituents of this nervous system is chromaffin substance or adrenal medulla.

That fatalities result through failure to recognize the adrenals in this connection is demonstrable by many instances on record. During *chloroform anesthesia*, for instance, the use of adrenalin both by injection and locally, the latter in the nasal *cavities, has caused so many deaths that various operators have* condemned its use. *And yet, a much larger number advocate its* administration both as a preventive of heart failure and to counteract this condition. Such contradictory opinions are due to disregard of available knowledge on the question, and the empirical use of this powerful agent. During the early stage of anesthesia, the adrenals, reacting against the toxic effects of chloroform, and under the influence of excitement or fear, secrete abnormally and increase peripheral resistance by causing constriction of the arterioles, including the coronary terminals, as shown by Barbour and Prince.[26] If adrenalin is now injected, it so increases this vascular constriction that notwithstanding the rise of blood-pressure, there occurs failure of the pulse, pallor, dilatation of the pupils, ventricular fibrillation and cardiac arrest—all due to inadequate supply of arterial blood to the ventricles, thus weakening their contractile power, while the increased resistance of the blood column tends further to prevent contraction and to arrest the heart in diastole. When, on the other hand, adrenalin is administered late, particularly *where heart failure threatens,* it compensates for the deficiency of this principle both in the adrenals themselves and in the sympathetic system, after its excessive secretion during the first stage for the reasons mentioned. Indeed, in heart failure attending chloroform anesthesia, Delbet, Herrenschmidt and Beauvy[27] and others, found marked diminution and even disappearance of chromaffinity and of adrenin itself in the medullary portion. Administered under these conditions, adrenalin is not only free from danger but often saves life as shown by a large number of cases in the literature on anesthesia.

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[*] In 1904[25] personal researches tended to show that the vagus owes its action on the heart to sympathetic fibers.

[25] C. E. de M. Sajous: N. Y. Med. Jour., lxxix, 913, 976, 1904.

Another feature of major importance in this connection, one likewise overlooked in cardiac disorders of the adynamic type is the influence of age upon the activity of the adrenals, *i.e.,* the *senile heart.* This is well shown in the plate opposite page 88 in this volume, which represents the vascular supply of the adrenals at various ages, the organs having been injected with a hardening substance, and the parenchyma then destroyed with a corrosive. Dostojewski, Rolleston[28] and others have likewise noted considerable reduction in the size of the adrenals in aged subjects. As all this means also a corresponding deficiency of adrenin in the sympathetic system, it becomes evident that in the elderly, uncomplicated cardiac dilatation or defective compensation in valvular disorders with asthenia, hypotension, hypothermia, and a tendency to collapse in marked cases, hypoadrenia should be taken into account. It is in such cases that our usual remedies fail, while the judicious use of suprarenal products is very efficient in appropriate cases.

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[26] Barbour and Prince: Jour. Exper. Med., xxi, 330, 1915.
[27] Delbert, Herrenschmidt and Beauvy: Revue de Chir., xlv, 544, 1912.
[28] H. D. Rolleston: Lancet, i, 727, 1895.

Here, again, considerable circumspection is required in the use of adrenal extractives. In the hypoadrenia of old age or in middle aged or young, the usual doses employed are safe. This ceases to be the case, however, when an active febrile process prevails, or when the subject treated is hyperadrenic as in plethoric subjects, and particularly where a valvular lesion exists. Here we must recall the principle established experimentally by Hoskins and McPeek[29] to the effect that an injection of adrenalin will augment any physiological action that the normal circulating adrenin in a given case might be producing. Precisely as it does during the early stages of chloroform anesthesia—and this applies as well to ether anesthesia though to a less marked degree—the peripheral arterioles and the coronary terminals will become abnormally contracted and expose the heart. This is well illustrated by the radioscopic study of one hundred cases by Loeper, Wagner and Dubois-Roquebert.[30] On injecting 1 milligram ($^1/_{60}$ grain) of adrenalin, these internists found that a normal heart showed no change in outline or slight contraction in one hour; a weak heart or one having a valvular lesion, dilated at once and remained so some time; a mitral lesion showed a particularly pronounced dilatation, while aortic insufficiency sometimes caused dilatation of the aorta. This coincides with the untoward effects credited to adrenalin by various clinicians, which occurred in patients showing valvular lesions. But this does not apply to cases in which hypoadrenia and broken compensation or functional dilatation prevail even with edema which also is benefited by suprarenal products.

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[*] The term "hypoadrenia" is used instead of "hypoadrenalism," because the latter wrongly infers the presence of a habit instead of what it is, a pathological condition. Since I introduced the former in 1903, many authorities employ it.

[29] Hoskins and McPeek: Jour. Amer. Med. Assoc., lx, 1777, 1913.

[30] Loeper, Wagner and Dubois-Roquebert: Le Progrès Médical, xxxiii, 83, 1918.

The *arrhythmias* are likewise dependent in many instances upon the efficiency of the adrenals, *i.e.*, when they are the expression of deficient nervous control of the myocardium or myocardial atony, irrespective of any causal organic lesions. They may occur in the course of *acute infections* owing to the hypoadrenia occurring late in these processes; or in DaCosta's "*irritable heart*" of soldiers (1871) in which emotional stress and excessive exertion likewise exhaust the adrenals; or, again, as a chronic condition in civil life in *neuro-cardiac asthenia*, such as that noted in masturbators (spermin containing a catalyzer which gives the reactions of adrenalin), excessive smokers (nicotine, but only in excessive doses being an adrenal depressant), the true "*adolescent heart*" due to tardy development of the adrenals, and many of the cases of "functional heart disease" —all of which are distinguishable by their frail make up, their sensitiveness to cold (deficient oxygenation), their myasthenia, dyspnea on exercise, and other symptoms denoting functional hypoadrenia. All of these show, besides a rapid heart rate, more or less irregularity at times. Indeed, Stewart and Rogoff[31] found that compression of the adrenal veins caused arrhythmia, which ceased when they released the veins, thus restoring the flow of adrenin to the inferior vena cava, the blood of which carried it to the right auricle and ventricle.

In *auricular fibrillation*, in which the auricle is unable to contract, the fluttering tremor which replaces contraction is attributed to a multitude of unexplained unco-ordinated impulses; but this phenomenon finds its explanation in deficiency of the adrenal chromaffin-substance. When, as in toxic cases, digitalis finally fails, it is because the adrenals themselves have failed. Adrenalin at this time, 8 minims of the 1:1000 solution in a syringeful of saline solution, injected intramuscularly very slowly, repeated as needed, proves very helpful. Even where, as in a personal case, dilatation of the peripheral arterioles, due to adrenal failure, causes peripheral edema, and digitalis ceases totally its beneficial action, both the edema and arrhythmia may disappear under the influence of adrenalin. Triturates containing $^1/_{60}$ grain may be allowed to dissolve under the tongue where injections cannot be used. To sustain the effect after recovery, 2 grains of the suprarenal gland twice daily, is very helpful as adjuvant.

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[31] Stewart and Rogoff: Jour. Pharm. and Exper. Therap., xiii, 397, 1919.

The same remarks apply to *auricular flutter*, often observed among the elderly and which may also be attended with dyspnea, myasthenia, edematous infiltration, etc. In *heart block* and the *sinus arrhythmias*, however, the causal lesions are probably localized in their bundle or node. So far at least, no benefit has been obtained from suprarenal products. The tachycardia noted in the course of these arrhythmias should be carefully differentiated from that due to hyperthyroidism.

PULMONARY DISORDERS.—Lobar pneumonia is another disease in which the mortality has failed to be reduced notwithstanding the great amount of study devoted to it. As in arteriosclerosis, this also appears to be due to the fact that, with the endocrins as factors in the problem, it is divisible into two or more types each of which requires its special line of treatment.

Senile pneumonia, now classed among the so-called atypical cases, will serve to illustrate this statement. It was termed by Charcot "the great enemy of old people"; Osler, referring to subjects over sixty years of age, stated that "from its fatality in some places one may say that to die of pneumonia is almost the natural end of old people." Senile pneumonia may drop upon an aged subject and prove fatal unexpectedly right in the midst of his daily occupation. Where, however, as in most instances, the disease develops more or less gradually, typical symptoms of adrenal failure appear. After a brief reaction to the infection, with practically no fever or elevation of the pulse, very moderate rise of blood-pressure, no chill other than perhaps a chilly sensation, but little, if any cough and expectoration and no pain in the chest, there occurs rapid lowering of the arterial tension, marked lividity, edema of the lungs and extreme asthenia with lethal trend from exhaustion. The influence of deficiency of adrenin on the right ventricle whose tone it sustains as it passes on to the lungs, is well shown by Elsner's statement[32] that "dilation of the heart, particularly of the right side, is a frequent complication of senile pneumonia," but this clinician also records a fact of cardinal importance, namely, that the dilatation of the right heart "sometimes *precedes* the infection" which means that the infection itself may be secondary to the adrenal failure. The pulmonary edema which virtually drowns the sufferer, results from the vascular paresis, due likewise to deficiency of adrenal principle, which as shown by Plumier-Clermont,[33] sustains the tone of the pulmonary vessels to a degree less marked than elsewhere throughout the body.

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[32] H. L. Elsner: N. Y. State Med. Jour., ix, 34, 1909.

On the whole, the senile adrenals either fail soon after the infection, or by suddenly giving way and reducing the resistance to infection, permit the lungs to become the prey of the pneumococcus or other ubiquitous bacteria. That these organs fail increasingly as age advances is well shown in the plate opposite page 88.

The treatment of such cases should differ totally from that usually employed. From the start, when the symptoms of adrenal failure prevail, repeated doses of 7 minims of adrenalin 1: 1000 solution in a syringeful or more of saline solution should be injected intramuscularly very slowly, carefully avoiding a vein, every two hours three times, when the blood-pressure is low, then, when the heart action and the blood-pressure have improved, four times a day, as needed until they are normal. Perpetuation of the good effects is sometimes better insured by injecting 4 minims of adrenalin and 4 minims of pituitrin at a dose, the main effect of the latter being due to the adrenal principle in organic combination it contains. The oral use of these agents, or a triturate pellet of $^1/_{60}$ grain, placed under the tongue, in addition, is often helpful. As stated by W. E. Robertson,[34] "it is well known that cases that react are more favorable than those with low temperature. This is universally recognized in senile pneumonia."

When the patient's defensive resources do not improve after a few adrenal or pituitrin injections, the use of antipneumococcus serum is indicated, besides sustaining food in small quantities frequently repeated, warmth with pure but not cold air, and creosote carbonate to prevent tympanites, avoiding all depressants, particularly bleeding, nitrites and opiates. This treatment affords far better results in this form of pneumonia than the present random and often misdirected measures.

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[33] Plumier-Clermont: Bull. de l'Acad. Royal de Méd. de Belg., xxvi, 596, 746, 1912.

[34] W. E. Robertson: Lectures at Temple University, Phila.

Bronchial Asthma.—The effects of adrenalin in this disorder further illustrate the functional relationship between the adrenals and the respiratory process. The dominant view concerning the underlying cause of asthmatic paroxysms is that an accumulation of endogenous wastes, due to deficient catabolism, provokes spasm of the bronchial and thoracic muscles. The asphyctic phenomena thus produced last until the tidal wave of toxic wastes is in part hydrolyzed through the effects of a defensive reaction. As such a reaction primarily depends upon the activity of oxygenation, while the adrenal secretion, as we have seen, endows the hæmoglobin with its power to take up oxygen from the air, an injection of adrenalin fulfills this purpose. It does more; Fühner and Starling[35] found that in asphyxia the heart dilates and the aortic pressure falls, thus reducing both the pulmonary and general circulation, and that both these conditions were relieved by adrenalin. Again, we know that asphyxia neonatorum may at once be relieved, as shown by Mack,[36] by injecting adrenalin into the stump of the cord. In asthma, the cyanosis frequently observed bespeaks a carbon dioxide retention in keeping with the views of many writers. While, as we have seen, Bernstein and Falta[37] found that injections of adrenalin produced an increased consumption of oxygen, and of carbonic acid excretion, Januschke and Pollak[38] observed that they caused an increase in the respiratory excursions of the lungs. Every phase of the morbid process is thus met by adrenalin, the action of which is truly striking as regards efficiency in appropriate cases.

The use of adrenalin, however, for the arrest of asthmatic paroxysms is not free of danger, owing to the fluctuations of the adrenin content in the individual treated. Particularly, are untoward effects—cyanosis, tremor, pallor, thoracic constriction, weak pulse, etc.—produced when it is injected hypodermically or intravenously, while its intramuscular use in 8 minims (0.5 cubic centimeter) of the 1: 1000 solution is very seldom attended by any ill effect, especially if administered slowly with a syringeful of saline solution. Advanced valvular disorders, cardiac hypertrophy and nephritis with high blood-pressure are contraindications.

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[35] Fühner and Starling: Jour. of Physiol., xlvii, 286, 1913-1914.
[36] A. E. Mack: Jour. Amer. Med. Assoc., lxv, 794, 1915.
[37] Bernstein and Falta: *Loc. cit.*
[38] Januschke and Pollak: Archiv f. exper. Path. u. Pharm., lxvi, 205, 1911.

Renal Disorders.—The relationship between functional efficiency of the adrenals and renal activity is well shown by the effects of adrenalin in cases in which *anuria* occurs irrespective of any discernible diseases as a result of asthenia, shock, etc. This may be observed particularly in aged subjects in whom, we have seen, the adrenals undergo progressive atrophy. In such, all the usual remedies, including strychnine, a powerful adrenal stimulant as previously shown, fails to promote diuresis, but this result soon follows the use of adrenalin, and persists as long as this agent is administered. In the light of the prevailing view that adrenin causes renal dilatation, this is due to constriction of the peripheral arterioles (previously relaxed owing to adrenal insufficiency) by the adrenalin and restoration of the normal circulatory tension in the renal filter. This explanation is further sustained by the fact that, as observed experimentally by Hoskins and Gunning,[39] marked renal inefficiency follows adrenalectomy, and the confirmation by Hartman and Lang[40] of the view that dilatation of the kidney is caused by adrenalin, although this is preceded by brief constriction of the organ.

Restoration of the tonus of the peripheral arterioles and, as a result, of the normal vascular tension, likewise explain the very marked influence of adrenalin upon the edema of renal origin, as will be shown, but the adrenal principle has also been found of value in the various forms of nephritis. Other influences of adrenal origin must therefore prevail.

Confirming the older experiments of Siegel, Reicher[41] found that a ten-minute immersion of the back paws of animals in ice water caused within ten minutes an increase of adrenalin in the blood, and within twenty-four hours albumin and casts in the urine. This increase of adrenalin in the serum has also been observed by Schur and Weise and also by Goldzieher and Molnar[42] in both *acute* and *chronic* types of *nephritis*. R. M. Pearce,[43] in a study of 163 adrenals, also found that hyperplasia of these organs was a very frequent concomitant of chronic renal disease, thus sustaining the previous observations of Aubertin, Ambard, Widal, Boidin and Vaques,[44] who had noted hyperplasia of the adrenals in all cases in which atrophy of the organ had occurred, which they traced back to the initial stage of the disease, and which, they state, cannot be confounded with fatty adenoma. Baduel[45] found that both the cortex and medulla were the seat of hyperplasia.

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[39] Hoskins and Gunning: Amer. Jour. of Physiol., xliii, 298, 1917.
[40] Hartman and Lang: Endocrinology, iii, 321, 1919.
[41] K. Reicher: Berl. klin. Woch., xlv, 1435, 1908.
[42] Goldzieher and Molnar: Budapest Corresp. London Lancet, ii, 124, 1908.
[43] R. M. Pearce: *Loc. cit.*

The connection between the abnormal increase of adrenalin in the blood and all grades of nephritis has remained obscure. From my viewpoint, however, the explanation is to be found in the adrenal functions we have reviewed, *i.e.*, a defensive reaction calculated to break down the pathogenic factors which impair the renal tissues similar to that which occurs in infectious diseases, the adrenal overactivity being perpetuated as long as the harmful substances are present in the blood. The influence of the adrenals on oxygenation and metabolism is not only an integral feature of the defensive process in this connection, but also of the functional efficiency of the kidney itself. When the adrenals finally fail, edema begins to appear owing to relaxation of the peripheral arterioles, whose tonus the adrenal principle sustains.

This accounts for the marked benefit reported particularly by Italian clinicians from the use of adrenalin. As far back as 1897, Concetti,[46] both in acute and chronic nephritis, obtained gradual but permanent disappearance of the albumin, increased diuresis and urea excretion, disappearance of the edema and of the general symptoms. Paoloantonio[47] found the oral use of 2 to 3 minims of the 1 : 1000 solution of adrenalin per year of the child's age, of considerable value in the glomerular nephritis of scarlet fever and recommends particularly in the acute forms. Ercolani[48] used as much as 60 minims daily in elderly uremics without untoward effect. Harris[49] obtained similar results where the usual methods produced little or no benefit. Personal experience confirms these observations and has tended to show that adrenal efficiency materially influences renal activity.

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[44] Vaquez: Trans. Soc. med. des Hôpitaux, Semaine méd., xxv, 369, 1905.

[45] A. Baduel: Rivista Critica di Clin. med., ix, 485, 501, 1908.

[46] Concetti: Trans. 12e Cong. internat. des sci. med., Rev. mens. des Mal. de l'Enfance, xv, 476, 1897.

[47] D. Paoloantonio: Policlinico, xx, 1751, 1913.

[48] P. Ercolani: Gaz. degli Osped. e della Clin., xxxviii, 353, 1917.

[49] I. Harris: Liverpool Med.-Chir., xxxvi, 85, 1916.

ASCITES AND OTHER SEROUS EFFUSIONS.—Osler characterized a type of chronic interstitial nephritis the "senile form" of contracted kidney, but as shown in the plate opposite page 88, there is also atrophy of the adrenals in old age. With normal kidneys, no serous effusion occurs; where, however, contracted kidney is present *plus* adrenal atrophy and broken compensation (the heart and its sympathetic supply being likewise dependent for efficiency upon adrenin) ascites follows.

Sir James Barr, in 1903, introduced the use of adrenalin injections in effusions, having obtained rapid diminution and, in some instances, arrest of this complication in pleural, pericardial, hepatic and peritoneal disorders. These results were confirmed by other observers, where, as in cirrhosis, cancer, etc., the morbid process was not too far advanced, or a mechanical obstructive factor did not prevail. In ascites of cardiac origin due to failure of compensation J. C. Voigt[50] among others, obtained marked diuresis, disappearance of the dropsy, from injections of 5 to 15 minims of adrenalin chloride 1 : 1000 solution, the effect being sustained by the oral use of 5 grains of the desiccated suprarenal gland. Similar results have been obtained by numerous observers in pleurisy with effusion after removal of the latter.

Tyson and Jump[51] observed a case of chronic nephritis with mitral regurgitation and ascites in which repeated tapping followed by intraperitoneal injections of from 8 minims to 2 drams of the adrenalin chloride 1 : 1000 solution, caused a marked increase of the urine secreted and eventually disappearance of the ascites. Fleisher and Loeb[52] had previously obtained similar results, and observed an "increase in the osmotic pressure of the blood" doubtless due to the increased constriction of the peripheral arterioles caused by the epinephrin. Plant and Steele[53] noted another significant effect of the adrenalin solution: "In all cases," they state, "there was a rise of from 0.5 to 2.0 degrees of temperature," also "an immediate rise in the pulse tension." Finally, as is well known, localized edemas, pharyngeal, laryngeal, etc., are promptly relieved by a solution of adrenalin, owing to the constriction of the arterioles it causes.

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[50] J. C. Voigt: Brit. Med. Jour., i, 536, 1912.
[51] Tyson and Jump: Therap. Gaz., xxxv, 10, 1911.
[52] Fleisher and Loeb: Jour. Exper. Med., xii, 288, 487, 1910.
[53] Plant and Steele: Brit. Med. Jour., ii, 125, 1906.

General Infections.—Failure of the adrenals as a result of an infectious disease is perhaps best exemplified in its most acute form by *Asiatic cholera.* In 1903, I[54] called attention to the striking similarity of the symptomatology of this disease to that of complete adrenal failure. Since then several authors, Drake-Brockman (1910), Plovcsana (1912), Naamé (1914) and others, have emphasized the same kinship in epidemics, all using adrenalin in large or frequently repeated doses with beneficial results. Naamé,[55] in fact, observed a remarkable tolerance for adrenalin in these cases, preferably administered with saline solution. The syndrome of acute hypoadrenia is strikingly reproduced: The typical peripheral hypothermia, the high rectal temperature, the frigidity and cyanosis, the rapid often intermittent pulse, the marked asthenia, etc. The pathogenic relationship between the two processes was studied experimentally by Demetrescu,[56] who found that the cholera endotoxin caused in rabbits disappearance of the chromaffin substance from the adrenals, thus accounting for the phenomena witnessed. During the recent war, *choleraic diarrhea* was often observed in troops which had been subjected to great fatigue and especially in men who had been called to the colors from sedentary life. The pathogenesis of such cases is clear when the relationship between the adrenals and general oxygenation and metabolism is recalled; briefly the glands were sufficiently exhausted to approach the condition they presented in Asiatic cholera. Satre and Gros,[57] who called attention to this disorder during the war, found that adrenalin soon overcame it.

By far the most frequently encountered instances of adrenal failure are those observed late in the course of practically every infectious disease when the morbid process is severe or prolonged. In *typhoid fever* it is commonly observed, the disease assuming what has been termed the "cardiac type," in which great prostration, low blood-pressure, hypothermia, sweating, weak and rapid pulse—all typical symptoms of slowed metabolism and vascular failure of adrenal origin—predominate. It is also common in *pneumonia* and *bronchopneumonia*, *influenza*, *pernicious malaria*, and not infrequently in *scarlatina*, *measles*, *septicemia*, *erysipelas*, *anthrax* and *gaseous gangrene* as shown during the war. This important phase of severe infections, and its life saving value have been recognized to such a degree in France, particularly through the labors of Letulle, that many practitioners anticipate the occurrence of adrenal failure by using adrenalin prophylactically, *i.e.*, prior to its expected onset. Thus, Josué[58] administers 1/60 grain (0.001 gramme) in 1/2 to 1 pint (250 to 500 cubic centimeters) of saline solution by hypodermoclysis. Being absorbed slowly, the action of the adrenal principle is sustained.

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[54] C. E. de M. Sajous: Internal Secretions and the Principles of Medicine, i, 30-52, 772, 1903; ii, 1720-1730, 1907.

[55] M. Naamé: Presse méd., xxii, 725, 1914.

[56] C. A. Demetrescu: Bull. sect. scient. de l'Acad. roumaine, iii, 225, 1914-1915.

[57] Satre and Gros: Progrès méd., xxxiii, 205, 1918.

It is important to bear in mind in this connection that large doses of adrenalin predispose to *adrenal apoplexy* particularly when injected intravenously. This question was carefully studied by S. M. Mansvetova,[59] who found that 1 cubic centimeter (16 minims) of adrenalin injected subcutaneously in various acute infections, caused a sudden rise of pressure with but a slight increase of the amplitude of the pulse; 0.75 cubic centimeter (12 minims) produced less rise in pressure but greater pulse amplitude both on account of increased systolic and lowered diastolic pressure; 0.5 cubic centimeter (8 minims) did not apparently cause any constriction of the peripheral blood vessels. This corresponds with my own experience, which has shown that 8 minims of adrenalin in a syringeful of saline solution injected intramuscularly, very slowly, gave the best results and could be administered four times in twenty-four hours, if need be, when the signs of adrenal failure began to appear, without fear of untoward effects.

Considerable care in diagnosis is necessary, therefore, to avoid administering adrenal extractives where they might actually cause death. *Bacillary dysentery*, for instance, was also found during the war occasionally to lead to a condition suggesting algid cholera. In reporting four such instances in one hundred men suffering from bacillary dysentery Remlinger and Dumas[60] observed four who suddenly showed severe abdominal pains, hypothermia, cyanosis, and all the signs of Asiatic cholera and soon died. In each case the autopsy showed that the adrenals were the seat of lesions which complicated the existing infection and caused the glands suddenly to become the seat of hæmorrhage, thus constituting what Boinet has termed "adrenal apoplexy" and soon followed, as a rule, by death. It may occur in practically any infection, *pneumonia,* as in a case recently reported by Löwenthal,[61] *tuberculosis, Addison's disease,* usually due to tuberculosis of the adrenals, *meningitis, abscess,* etc., and disorders which tend to raise the blood-pressure, such as *epilepsy, arteriosclerosis, chronic renal disease,* etc.

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[58] M. O. Josué: Trans. Soc. de biol., Paris méd., v, 540, 1915.
[59] S. M. Mansvetova: Rousskii Vratch, xiii, 874, 1914.

Adrenal apoplexy occurs not infrequently in infants, especially those which show patches of *purpura,* and is frequently overlooked as a cause of death. In such cases adrenalin in the usual doses may kill by raising the blood-pressure, as shown by several instances reported. Conversely, in such cases, vascular depressants, the nitrites, veratrum, chloral hydrate, etc., enteroclysis, or in threatening cases, hypodermoclysis, to reduce the viscidity and promote osmosis, will lower the vascular tension and avert the danger.

THE THYROID GLAND IN ITS RELATIONS TO DISEASE AND TREATMENT.

The rôle of the thyroid in metabolism will be fully studied elsewhere in the present work. As to the scope of its influence both in health and disease, it is fittingly summarized by Kendall's remark that: "The changes occurring in a patient with thyroid deficiency or in an experimental animal, by the administration of thyroid are so great that practically every cell within the organism is changed. The effects are felt throughout the nervous system and the circulatory system; the rate of metabolism is enormously increased." The articles on the diseases of the gland, especially hyperthyroidia* will further emphasize its activity as a catabolic stimulant. Of additional interest when its influence in nutritional diseases is taken into account, however, as first shown by Horsley in 1892,[62] and confirmed by Vassale, Blum and others, is that this catabolic action includes the breaking down of toxic products of metabolism, *i.e.*, the detoxicatory rôle of the gland.

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[60] Remlinger and Dumas: Annales de méd. de Paris, ii, 605, 1914-1915.

[61] K. Löwenthal: Berl. med. Woch., lv, 1128, 1918.

* Throughout this work I have used "hyperthyroidia" and "hypothyroidia" in preference to "hyperthyroidism," etc., not only because the latter falsely suggests a habit rather than a pathological condition, but also because it corresponds with the terminal "ia," "ie," etc., used in other languages and is the more correct.

The theory that the thyroid formed part of our immunizing mechanism, *i.e.*, our defensive functions against infections and exogenous pathogenic agents was introduced by myself in 1903, and further developed in 1907 in the early editions of the present work.[63] Briefly, it postulated that, in conjunction with the products of other glands, notably the adrenals and pancreas, the thyroid formed an autoantitoxin in which the thyroid secretion filled the rôle of bacterial *sensitizing agent*, such as that described by Denys and Leclef and which Sir A. E. Wright and Douglas termed "*opsonin*." This view has been repeatedly sustained in Europe. Fassin[64] in the Bacteriological Institute of Liége, Belgium, and Marbé[65] at the Pasteur Institute, both found—the latter in 116 examinations—that removal of the thyroid gland "showed in every instance a most evident diminution of opsonic power," while Stepanoff,[66] also at the Pasteur Institute, observed "elevation of the opsonic index after injections of thyroid extract in rabbits." All three concluded, furthermore, that the thyroid played an important rôle in immunity, Stepanoff's experiments bearing mainly upon the tubercle, diphtheria and coli bacilli, the staphylococci and streptococci. Orth,[67] in three instances of thyroidectomy for goiter, observed sudden aggravation of moderate tuberculosis soon followed by death, and refers to Clairmont as having reported similar observations in tuberculosis. Barbara[68] also concluded after experimental studies that the thyroid was an important factor in the defensive function of the body against infection, having found among other facts, that thyroidectomy caused immunizing agents, complement, opsonins, etc., and phagocytosis to be notably reduced. Koopman,[69] of the Hague, in experiments on rabbits, found that thyroid therapy increased gradually the antibodies in the animals showing hypothyroidia—an observation frequently confirmed by practical experience. Finally, omitting much additional evidence, Lieut.-Colonel McCarrison,[70] who has contributed likewise much to our knowledge of this function, states in a review of the whole question beginning with my labors: "The fact that the antitoxic and bactericidal resources of the body are largely dependent on the functional perfection of the thyroparathyroid mechanism is, I believe, as clearly established as is the influence of this mechanism on metabolism."

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[62] V. Horsley: Brit. Med. Jour., i, 215, 265, 1892.

[63] C. E. de M. Sajous: Internal Secretions and the Principles of Medicine, i, 609-665, 728-778, 1903; ii, 1037-1087, 1907.

[64] L. Fassin: C. r. de la Soc. de Biol., Paris, lxii, 388, 467, 647, 1907.

[65] Marbé: *Ibid*, lxiv, 1113, 1908.

[66] M. Stepanoff: *Ibid*, lxvi, 296, 1909.

[67] Oskar Orth: Deut. Zeit. f. Chir., cxlviii, 360, 1919.

[68] M. Barbara: Annali di Clin. Med., ix, 1, 1919.

The importance of this defensive mechanism in everyday diseases is shown by the manner in which the thyroid gland reacts under the infectious diseases. In 1888, long before any connection with the processes of immunity was thought of, Hale White[71] had called attention to the fact that this organ showed histological changes in acute infections. Roger and Garnier[72] then noted that scarlet fever, measles, diphtheria, small-pox, typhoid fever, cerebrospinal meningitis and septic peritonitis, tuberculosis, lobar pneumonia and septicemia, which represented the entire series of the diseases in which the thyroid had been examined by them, all caused in the organ either congestion or hypertrophy with increased secretion, while in seventeen cases in which death had been caused by non-febrile diseases, the thyroid showed no histological changes. These observations have been repeatedly confirmed by other investigators in various countries. Notable among these was Farrant[73] who in 1913, found that while thyroid feeding failed to produce hyperplasia of the gland, this condition attended the various diseases of children. A comprehensive study then showed that, besides the diseases enumerated above, those which produced thyroid hyperplasia were, bacillus coli infections, meningococcic infections, actinomycosis, acute anterior poliomyelitis, rheumatic fever, syphilis, chronic nephritis, pernicious anemia, anthrax, dysentery, tetanus, glanders, malaria, bronchopneumonia, disorders due to the B. enteridis and to micrococcus catarrhalis and hepatic cirrhosis. It now became a question as to whether the hyperplasia was not itself a morbid result of the disease present. He found, however, that besides the action on the gland of diphtheria as a disease, "repeated injections of diphtheria toxin lead not only to the production of thyroid hyperplasia but also to the formation of antitoxin," thus confirming directly my earlier contention.

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[69] J. Koopman: Endocrinology, iii. 318, 1919.
[70] R. McCarrison: Lancet, i, 365, 1913.
[71] W. Hale White: Trans. Royal Medico-Chir. Soc., London, lxxi, 181, 1888.
[72] Roger and Garnier: Presse méd., vi, 181, 1899.
[73] Rupert Farrant: Brit. Med. Jour., ii, 1363, 1913.

Additional evidence is afforded by the multiplicity of disorders in which, as we all know, iodine and the iodides are employed with good results, even though their mode of action had remained obscure. Hare,[74] for instance, writes: "The physiological action of iodine, so far as its alterative powers are concerned is absolutely unknown." Concerning the iodides, Cushny[75] likewise states: "Their mode of action is still wrapped in mystery." This obscurity disappears, however, when we recall that the active agent of the thyroid hormone is iodine in organic combination. Thus, Marine[76] found experimentally that thyroid tissue possessed extraordinary affinity for iodine, as high as 18.5 per cent. of a given intake of this halogen given by mouth being recoverable from a thyroid whose ratio to the body weight is as 1 to 687. It absorbs iodine according to its size and the degree of hyperplasia present, until its capacity to do so is reached. Clinical data show also that when this limit, which varies not only in different individuals, but often in the same individual, has been reached, iodism appears if iodine in any form is administered in excess of the ability of the normal gland to convert it into its own product. Its protection seems to begin in utero; as shown by F. Fenger,[77] iodine is present in the gland long before birth, the proportion increasing as the fetus approaches term.

On the whole, the invaluable property of iodine and the iodides we have classified temporarily under the term "alteratives" should be credited to the thyroid secretion owing to its active participation in our immune chemistry. The rise of temperature and the rapid pulse we observe in acute infections are indications that the defensive reaction in which the thyroid body takes part is actively fulfilling its physiological rôle. Experience the world over has now shown that death hovers over the sufferer whose defensive resources, through exhaustion, advanced age, syphilis, etc., are unable to react defensively, as shown by a low temperature.

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[74] H. A. Hare: Text-book of Practical Therapeutics, Phila., 15th ed., 300, 1914.
[75] A. R. Cushny: Pharmacology and Therapeutics, Phila., 7th ed., 391, 1918.
[76] David Marine: Jour. Biol. Chem., xxii, 547, 1915.
[77] F. Fenger, *Ibid*, xi, 489, 1912.

In the light of the foregoing facts, the temperature and basal metabolism do not only serve to indicate a febrile state or hyperthyroidism, but they jointly furnish an index of the efficiency of the systemic protective mechanism against infection. This may be emphasized by the hypothyroid syndromes in which vulnerability to infection is characteristic.

The most exaggerated expressions of this condition are, as is well known, the syndromes known as myxedema and cretinism which will be described in full in the section upon the diseases of the thyroid gland. What the practitioner often meets in his daily work, however, is a *larval type of hypothyroidia,* varying in degree almost with each patient, and which underlies the pathogenesis of many chronic disorders, general and local. In this form, the thyroid apparatus supplies a part only of the secretion required by the tissues, and the resulting phenomena recall closely some of those observed both in myxedema and cretinism: Chilliness and subnormal temperature, coldness of the extremities and sensitiveness to cold; fatigue on slight exertion; constipation with tendency to tenesmus; frequent attacks of *migraine,* "sick headaches" with nausea, vomiting, etc., and other periodic manifestations of autointoxication—due to inadequate reduction of waste products and their retention in the blood. The skin taking part in the process of elimination, *urticaria* and *eczema* are frequently observed, while transitory edemas of the brow, around the eyes, and sometimes of the face, even in the absence of albuminuria or casts, point to renal fatigue. *Enuresis* is commonly observed in children of this type and may persist to adult age. The patient is subject to frequent *catarrhal disorders* of the respiratory passages, usually ascribed to colds, but due mainly to vascular and glandular relaxation. A tendency to early *alopecia,* including the eyebrows (especially the outer third), is also noticeable—a sign of deficient general nutrition which coincides with a marked proclivity to early senility.

In women the menstruation appears late, owing to retarded development, and there is a proclivity to *metrorrhagia* due to laxity of the muscular coats of the uterine arterioles due to concomitant hypoadrenia, while pelvic disorders are apt to occur owing to deficient support of the uterus and lack of tone in its muscular elements. *Leucorrhea* is also frequent, owing to relaxation of the glandular elements of the whole genital tract. When such women conceive *abortion* frequently results; if the fetus is carried to the normal period, they have little or no milk. A few examples will now be submitted to illustrate the importance of the thyroid body in immunology.

RHEUMATIC DISORDERS.—In so far as the influence of the defensive functions is concerned, cretins and myxedematous patients are known to be particularly liable to infections of all sorts. In the larval forms of hypothyroidia, this liability is none the less marked, for as soon as the standard of protection falls below normal, as evidenced by hypothermia, which betokens slowed metabolism, the multiplication of bacteria is no longer hampered. In both the acute and chronic forms of articular rheumatism signs of hypothyroidia may often be discerned. While in some patients a myxedematous state is rendered evident by a puffy infiltrated and rough skin, crisp hair, a husky voice, mental dullness and torpor, low blood-pressure, hypothermia, deficient diuresis with low urea excretion, in others, the larval signs can alone be discerned: A tendency to cold feet and hands, a pasty skin showing transient edemas, scant hair, obesity, psoriasis, eczema or herpes, nausea, constipation and myasthenia—all sufficiently marked to place the cases in a category of their own, *i.e.*, those which resist the familiar methods of treatment.

Is the rheumatic process to be attributed to the hypothyroidia owing to the accumulation of wastes it entails in these cases? Were it so, *rheumatism* should occur at least frequently in cases of goiter showing the characteristic hypothyroid stigmata; but a study of one hundred of such cases by Mouriquand

and Crémieu[78] showed that a tendency to rheumatism was present in but 8 per cent. They found, moreover, that such cases failed totally to yield to even intensive treatment, 75 grains or more of sodium salicylate per day, for instance, along with other familiar agents. They also observed, however, that thyroid gland in small doses, 1½ grains or less per day, given in addition to the salicylates, relieved all acute symptoms promptly, in one instance within forty-eight hours, and led ultimately to recovery where many months of treatment by the usual methods alone had proven useless. The thyroid was undoubtedly the beneficial factor, for its withdrawal would promptly be followed by a recurrence of symptoms, while its resumption would as soon initiate steady improvement.

We have distinct evidence of the bactericidal or antitoxic influence of the thyroid product in this connection when we recall that focal infections are important etiological factors in all forms of rheumatism, polyarticular, muscular, acute or chronic. It is the concurrence of the infection with hypothyroidia which initiates and sustains the disease; the thyroid gland being unable to carry on its share of the defensive function, which is to sensitize the bacteria and their toxins preparatory to their proteolysis, their conversion into eliminable wastes is not accomplished. The salicylates in such cases play merely the rôle of analgesic by causing constriction of the arterioles which, while relaxed, had permitted hyperemia of the joints to occur and cause the local heat and swelling observed.

An essential feature of the use of thyroid products is that small doses only should be used. When first tried, they were found harmful, merely because of ignorance of their mode of action. This was long ago emphasized by the late H. C. Wood, Sr.,[79] who showed that doses of 3 to 5 grains could cause very severe articular rheumatism with edema. A single grain of desiccated gland twice daily usually suffices. Leopold-Lévi[80] has found that even smaller dosage, not more than 1½ grains three times a week gradually increased to one dose daily were curative. In some instances, minute doses, 1/60 grain, produced excellent effects, he states, where larger doses had failed. A peculiarity of the thyroid gland is that hypothyroidia occurs as soon as its secretion has just gone below the normal level, a fact which imposes the necessity of adjusting the dose to each patient. I have obtained considerable improvement even where the stage of *arthritis deformans* had been reached, where a causative infection could be found and eliminated—an important feature in all cases of articular rheumatism. Midelton[81] holds that very few cases of long standing arthritis fail to show some degree of thyroid failure. Important also in this connection, is the fact that atrophy of the thyroid progresses with old age precisely as is the case with the adrenals.

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[78] Mouriquand and Crémieu: Paris méd., iii, 444, 1911.
[79] H. C. Wood, Sr.: Phila. Med. Jour., i, 1012, 1898.
[80] Leopold-Lévi: Les doses en thérapeutique thyroidienne, Paris, 1-87, 1918.

PULMONARY DISORDERS.—The participation of the thyroid in our defenses against infection is also demonstrable in pulmonary tuberculosis.

We have seen that in 1903 and 1907, I had pointed out that the thyroid secretion was a constituent of the systemic antitoxin, its special rôle being that of opsonin and that this view had repeatedly been confirmed by others. In a study of experimental tuberculosis in guinea-pigs and rabbits, C. Frugoni[82] administered thyroid gland to these animals, and found both *in vivo* and *in vitro* that the opsonic index was markedly raised in them as compared with their controls. With Grixoni[83] the same observer had also found experimentally that the daily administration of thyroid gland at a time corresponding to or preceding infection with tuberculosis, and in such doses as are well borne, caused an energetic acceleration of the metabolism of the organism and modified favorably the action of the experimental tuberculous infection in rabbits. The animals treated with thyroid gland lived longer than the control animals, and in some cases life was prolonged indefinitely. G. B. Webb,[84] referring to experiments by Gilbert and himself, and remarking that *enlargement of the thyroid gland is very frequent in early cases of pulmonary tuberculosis,** whereas in late stages this gland would appear to share in the general atrophy, states that they removed from three-fourths to the whole of the thyroid gland in one set of guinea-pigs, and exposed but did not remove the same gland in controls. Four weeks later each pig of both series received a subcutaneous inoculation of forty living virulent human tubercle bacilli. They also found in two series of experiments (B and C) that the tuberculous pigs from whom the thyroids were removed died earlier and had more extensive tuberculosis than the controls, thus showing that the thyroid left *in situ* in the controls had evidently afforded protection in these two series.

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[81] W. J. Midelton: Practitioner, lxxxviii, 180, 1912.

[82] C. Frugoni: Il Tommasi, iv, No. 21, 1911; Abst. in Les Nouneaux Remédes, xxvii, 396, 1911.

[83] Frugoni and Grixoni: Berl. klin. Woch., xlvi, 1160, 1909.

[84] G. B. Webb: Jour. Lab. and Clin. Med., i, 414, 1915-1916.

* I emphasize this observation, confirmed by other observers, because Goetsch has recently advocated removal of the thyroid, disregarding its defensive rôle.

Yet in A series, from which three-quarters of the gland only had been removed by Webb, the result was quite different. While the control pigs, those in which the thyroid had been left, "were thin and emaciated and dying," the others, though deprived of a large part of their gland "were fat and healthy in appearance"! He also cites Launoy and Lévy-Bruhl's[85] observations in chickens infected with spirocheta gallinarum after removal of the thyroid, that thyroidectomy did not modify the infection, and then concludes that his own experiments "would seem to suggest that in tuberculosis in guinea-pigs the thyroid gland tends to hypertrophy but that any decided bearing on immunity processes is not detected." Why this discrepancy with his results in his B and C series?

Light from other directions justifies Webb's conclusions that the thyroid has no *direct* bearing upon the immune process *per se*. Fjelstad[86] found that removal of the thyroid from rabbits did not materially affect the formation of immune bodies and particularly the agglutinins, while Frugoni[87] noted in the experiments referred to above, that while the bacteriolytic bodies and agglutinins were practically similar to those in the controls, the opsonic index was notably raised in animals treated with thyroid preparations, thus facilitating the destruction of the tubercle bacilli. Briefly, the thyroid hormone does only what I attributed to it as *opsonin,* or *sensitizing substance* which renders micro-organisms vulnerable to the proteolytic destruction by phagocytes and in the serum (bacteriotropins) and resists heat up to 60 to 65° C.[88] In other words, it is not the immune body nor an agglutinin, although it may combine with these bodies and thus take part, as stated, in the defensive process.

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[85] Launoy and Levy-Bruhl: Annales de l'Inst. Pasteur, xxix, 213, 1915.
[86] C. A. Fjelstad: Amer. Jour. Physiol., xxvi, 72, 1910.
[87] Frugoni: *Loc. cit.*

All this has served to show, moreover, the importance of hypothyroidia in the genesis of tuberculosis. We may be saturated with immune bodies, complements, agglutinins, precipitins, etc., but if the pathogenic germs and their toxins are not sensitized, *i.e.*, prepared to be attacked by phagocytes and the proteolytic substances the serum contains, infection progresses regardless of these militant agents.

As is well known, vulnerability to tuberculous infection is characteristic of cases of hypothyroidism—a fact which explains Joseph Walsh's observation at the Phipp's Institute that "the only specific which has stood the test of time in tuberculosis is iodine." Although published sixteen years ago,[89] this remark still holds while tuberculin has virtually fallen by the wayside in the treatment of the disease.

Knowledge of the relationship between hypothyroidia and tuberculous' infection should enable us to forestall it. Indeed, in the presence or more or less adynamia, pallor, low arterial tension, weak cardiac impulse, sensitiveness to cold and gastro-intestinal discomfort, our mission should be to begin at once judicious iodine treatment, in order to increase the defensive efficiency and prevent infection. In such subjects, moreover, any degree of cough and emaciation should be looked upon with suspicion, and treated, in so far as the use of iodine preparations are concerned, without waiting for the appearance of tubercle bacilli in the sputum. The very large proportion of autopsies which show healed calcareous and sclerotic areas in the lungs—from 60 per cent. (Biggs) to 95 per cent. (Naegeli) of persons who had died of other diseases long after the pulmonary lesion had healed, betokens the awakening of *defensive hyperthyroidia* among other protective features, when the infection first occurred. This, with a little judicious assistance, might be caused to prevail in every case treated in time. Even where tuberculosis already exists the thyroid gland carries on its defensive rôle; Fujisawa[90] found that organs with tuberculous foci contained more iodine than all others.

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[88] C. E. de M. Sajous: Internal Secretions and the Principles of Medicine, ii, 1094, 1907.

[89] Joseph Walsh: Giorgia Pract., i, 171, 1905.

Important in this connection is the fact previously referred to, that the thyroid may become enlarged early in tuberculous infection and that removal of the gland under such conditions may greatly hasten the morbid process. Although I do not advocate thyroidectomy, because of the rôle of the gland in systemic immunity, excepting when a goiter is causing pressure or its systemic effects are growing dangerous to life, the fact remains that many think otherwise, notably surgeons. The differential diagnosis between a mild hyperthyroidia with goiter and enlargement of the gland due to tuberculous infection then assumes cardinal importance. Tuberculous cases before the pulmonary signs appear, are apt to undergo more rapid emaciation and to have a morning cough; the temperature remains above normal and may show an afternoon rise; the pulse is also rapid but steadily so and not influenced by trifles; there is no tremor. The enlarged gland is usually soft and compressible and soon begins to recede when iodine in any form is administered.

MENTAL DISORDERS.—In the catatonic form of *dementia præcox,* we witness, from my viewpoint, another phase of defensive activity of the thyroid, but exceeding as in Graves's disease, its normal bounds, to such a degree in fact, as to break down, in predisposed subjects, the phosphorized fats or myelins of the cortical and other neurons. This subject will be considered in full on page 325 and introduce besides personal labors, those of Fujisawa,[90] Berkley and Follis,[91] Kanavel and Pollock,[92] Dercum and Ellis,[93] Peabody,[94] Bayard Holmes,[95] Bornstein,[96] Dercum,[97] Jelliffe[98] and others.

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[90] Fujisawa: Mitteil. a. d. Med. Fakultät d. k. Univ. Tokyo, xix, 389, 1918.

[91] Berkley and Follis: Amer. Jour. Insanity, lxv, 415, 1908-1909.

[92] Kanavel and Pollock: Trans. Miss. Valley Med. Assoc.; Jour. Amer. Med. Assoc., liii, 1675, 1909.

[93] Dercum and Ellis: Jour. Nerv. and Mental Dis., xl, 73, 1913.

[94] A. H. Peabody: Boston Med. and Surg. Jour., clxiii, 196, 1910.

[95] Bayard Holmes: Trans. Lab. of Psychol. of Cook Co. Hosp., 202, 1918.

[96] A. Bornstein: Münch. med. Woch., lx-2, 1994, 1913.

[97] F. X. Dercum: N. Y. Med. Jour., civ, 289, 1916.

[98] S. E. Jelliffe: Trans. Amer. Congr. Internal Med.; Med. Rec., xci, 125, 1917.

THE PANCREAS IN DISEASE AND TREATMENT.

In its relations with disease, the pancreas, besides taking part in carbohydrate metabolism, supplies enzymes which also take part in protein metabolism as well in the systemic defensive functions, along with the adrenal and thyroid hormones. A study of the trophocytes of sponges, laboratory studies of the properties of ferments in lower forms, the migratory powers of leucocytes in higher forms, etc. (1903-1907) led me to conclude that some leucocytes, at least, migrated from the intestinal canal to the tissue cells, there to carry on, among other functions, that of proteolysis.

Abderhalden subsequently (1905-1915)[99] reached very similar conclusions. "Everything points," writes this biochemist, "to the fact that the [tissue] cell has agents at its disposal which render it capable of splitting up into their simplest units all the complicated substances which are brought to it or which it itself builds up" Again, "Each separate cell with very few exceptions disposes of the same or similar ferments as those secreted by the digestive glands in the intestinal canal." As to the manner in which the tissue cells are reached by these ferments, he writes: "Many facts accord with the suggestion that the leucocytes play a part in connection herewith." In keeping with my own views, Abderhalden has termed the digestive enzyme a "defensive ferment," thus bringing, he adds, "the so-called reactions of immunity into close line with processes that are normal and consequently familiar to the cells."

As to the actual presence of digestive enzymes in tissue cells, we may quote Mendel's statement[100] that "enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities in almost every feature of metabolism." Vaughan[101] also states that "the cell which can no longer supply a digestive ferment is already dead whatever be the kind or amount of pabulum surrounding it." As to the personal view that the blood was likewise the seat of a similar defensive process through the intermediary of trypsin, I may recall E. L. Opie's statement[102] that "the ability of the blood to remove injurious material is dependent on the possession of proteolytic enzymes. Peculiar to the polymorphonuclear leucocytes is an enzyme which, like trypsin, exerts its digestive action in an alkaline medium." Stocker[103] also states that any leucorrheal discharge contains a large number of polymorphonuclear leucocytes which are found to contain a proteolytic enzyme capable of digesting albumin, while Fiessinger and Clogne[104] found that these *secreted* an enzyme similar to that of pus leucocytes "whose action," they state, "resembles that of trypsin."

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[99] E. Abderhalden: Defensive Ferments of the Animal Organism, N. Y., 3d ed., 1914.

[100] I. Mendel: Med. News, lxxxvi, 913, 1905.

[101] V. C. Vaughan: Amer. Jour. Med. Sci., cxlv, 161, 1913.

What is the relationship between, on the one hand, the adrenal secretion, which we have seen, carries on tissue oxygenation, and the thyroid secretion which also markedly influences gaseous exchanges and takes part in the defensive process, and, on the other, the pancreatic enzyme trypsin which likewise is now shown to take an active part in this same defensive function? It appears to be as follows: Having traced the thyroparathyroid secretion to the lungs, where it entered the erythrocytes with the oxyhæmoglobin, I found that the blood platelets were secreted by the red cells. The thyroid product, or opsonin, in the immunological field, thus became, from my viewpoint, a part of the blood platelets. G. E. Webb[105] states that with Gilbert and Havens, he had reported experiments "which would indicate that blood platelets either carry or supply opsonins," thus confirming my conclusion. Trypsin, we have seen, is a constituent of leucocytes which, as many available data show, may also secrete their contents in the blood or in the tissues. In both these then (also in the phagocytes) the defensive process is as follows: Trypsin requires a temperature above normal to become *defensively* active (fever), its maximum efficiency being between 104 or 105° F.; this heat energy is provided by a process in which the oxygen-laden adrenin in the oxyhemoglobin is the most active factor. The opsonin having sensitized the germ, cell, toxin or waste product to be broken down, it is digested by the trypsin precisely as it would be in the alimentary tract.

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[102] E. L. Opie: Arch. Internal Med., v. 541, 1910.
[103] S. Stocker, Jr.: Gynecologia Helvetica, xi, 160, 1911.
[104] Fiessinger and Clogne: Annales de Méd. de Paris, 445, 1917.
[105] Webb, Gilbert and Havens: Arch. Internal Med., xiv, 743, 1914.

When all goes well and *normal fever,* the expression of active, but safe defense, prevails, the trypsic enzyme simply digests the pathogenic agent (in both blood and phagocytes) whatever it be, but when *hyperthermia* prevails, the digestive or proteolytic activity of the trypsin becomes excessive. It then includes in its digestive field the red corpuscles (hæmolysis), the vascular endothelium and the serosæ, peritoneal, pleural, pericardial, etc., the walls of which are richly supplied with blood-vessels (autolysis). The endocardium is another example of this morbid process and the present conception of *endocarditis* in this connection is so obviously the cause of the prevailing high mortality of this disease and its evil consequences, valvular disorders, that it was selected as an example of the pathogenic effects of the circulatory digestive enzymes when they are given, as they are now, full sway.

Cardiac and Valvular Disorders.—Under present conditions, malignant cases of *endocarditis* are practically always fatal, while in the less severe forms, the valvular and endocardial lesions so impair the functional efficiency of the heart as to favor an ultimate fatal ending. This is so marked that the mortality statistics of the 1914 Census refer to the deaths from organic heart disease as "the largest number classified under any of the titles in the international list of causes of death for that year." It states furthermore that "deaths from this cause exceed the number charged to tuberculosis of the lungs by more than 9000 and the number assigned to pneumonia (all forms), by nearly 10,000."

In the light of the foregoing data, and as I have long urged, this mortality is due in the main to the prevailing interpretation of the cardiovascular lesions in this disease. These, briefly, are attributed to the action of the bacteria themselves, a pure theory the truth of which no one has ever demonstrated. The pathogenic organism, whichever it be, may of course be found on the endocardium and on the valves, which they reach with the circulating blood. They may even, as shown by Rosenow, penetrate beneath the endothelium, carried therein in the blood of the capillaries, as shown by Bayne-Jones.[106] Yet, if bacteria are the direct factors in the process, how, for instance, account for the observation of Christian and Walker[107] that certain drugs also cause lesions of the endocardium, uranium, nitrate, potassium bichromate, arsenic in various forms, spartein and adrenalin given in succession? As is well known, glycosuria is caused by uranium, and likewise by pancreatic overactivity, under the action of the adrenal* and thyroid secretions, as shown under the next heading. Potassium bichromate is another active adrenal stimulant, its affinity for this agent being illustrated by the "chromaffin" reaction. The arsenates are noted for their "nitritoid" action which entails relaxation of arterioles and the admission of an excess of arterial blood into all organs, including the pancreas. Finally, spartein is likewise an adrenal stimulant, while adrenalin, as shown by Blum, Herter and others, causes glycosuria by exciting pancreatic action. In other words, all these agents, either directly or indirectly, are capable of enhancing the functional activity of the pancreas, and, by causing a defensive reaction of the adrenals and thyroid, thus accelerating oxygenation and by raising the temperature, of increasing the proteolytic activity of the trypsin secreted by the pancreas. As emphasized recently by Madsen,[110] phagocytic activity increases as the temperature rises, a fact which applies as well to the serum.

The production of endocardial lesions by certain drugs observed by Christian and Walker thus finds its explanation in the fact that the defensive enzyme rendered overactive by the increased oxygenation due to the adrenal stimulation and the epinephrin caused the endocardial lesions. This applies, from my viewpoint, to the endocarditis of bacterial origin as well, the many organisms, of which the streptococcus, staphylococcus aureus and gonococcus being probably the most active in this connection. Their presence upon or within the endocardial tissues causing them to be attacked defensively by the tryptic enzyme and phagocytes, both raised to excessive digestive efficiency by the concomitant hyperpyrexia, mainly of adrenal origin, after both germs and toxins have been sensitized by the thyroid hormone, the tissues themselves undergo proteolysis or digestion and break down. An acute local inflammatory process follows, attended by the formation of vegetations which eventually lead to the familiar lesions of the valves, chordæ tendinæ, etc.

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[106] S. Bayne-Jones: Amer. Jour. of Anatomy, xxi, 449, 1917.

[107] Christian and Walker: Trans. Amer. Soc. for Adv. of Clin. Investig., Boston Med. and Surg. Jour., clxii, 901, 1910.

* To advance at all in the study of the relations between the pancreas and disease, we must divest ourselves of the prevailing view advanced by Eppinger, Falta and Rudinger, and due to the experimental use of an excess of adrenalin that the adrenals either physiologically or pathologically inhibit the functions of the pancreas. As stated by Sollmann[108], "the theory is not based on good evidence." MacCallum[109] has likewise denied its correctness.

[108] T. Sollman: Manual of Pharmacology, Phila., 334, 1917.

[109] W. G. MacCallum: Jour. Amer. Med. Assoc., lvi, 655, 1911.

[110] M. Madsen: Trans. Soc. de Biol., Presse méd., xxvii, 127, 1919.

The treatment under these conditions should aim to reduce the proteolytic activity of the defensive ferment. This may be done by increasing the osmotic properties of the blood and its fluidity by the use of hypodermoclysis or in threatening cases, saline solution intravenously, with the free use of alkaline waters as beverage. Sodium bromide or veratrum viride are also useful to reduce the vascular tension and thereby the friction of the blood column upon the endocardium and valves. The bromides also promote rest and sleep, strict rest in bed being imperative. The ice bag over the heart and cold sponging tend likewise to limit the proteolytic activity of the blood enzymes by abstracting heat. Adrenal stimulants, digitalis, strychnin, strophanthus and epinephrin are absolutely contraindicated unless the case is seen when heart failure threatens. Even then it is preferable to first try camphor or aromatic spirit of ammonia and to resort to the former only when the latter fail.

All these facts apply equally well in their general lines to the diseases of the various serous membranes, *pleurisy, pericarditis, peritonitis*, etc.

METABOLIC DISORDERS.—*Glycosuria* follows removal of the pancreas and ceases if pancreatic tissue is successfully grafted even in some remote situation. As to how the pancreatic internal secretion causes glycosuria, Swale Vincent[111] writes: "We can only say that it exerts some influence upon the carbohydrate metabolism, either by favoring the formation of glycogen in the liver from the glucose taken to it by the portal vein, or by favoring the oxidation of glucose in the tissues generally."

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[111] Swale Vincent: *Loc. cit.*

In view of the rôle in oxidation I have attributed to the adrenals, these organs suggest themselves as factors in the process; this is further emphasized by the fact that Blum, Herter, Croftan and others produced glycosuria by injecting adrenal extract, while, as Claude Bernard, Kauffmann and others have observed, section of the splanchnics, which contain the secretory nerves to the adrenals, caused cessation of glycosuria. It is evident, therefore, that these organs take part in the morbid process. In the first edition of this work I pointed out that they did so under the influence of the familiar causal factors, including infections, mental stress, head traumatisms, excessive eating and drinking, etc., by becoming overactive. The pancreas being thus subjected to hyperoxygenation, its amylopsin, also secreted in excess, converts the tissue glycogen into sugar which the kidneys excrete as rapidly as they can. Hence the fact that, as stated by W. G. MacCallum, in the 1920 edition of his Pathology[112]: "In *diabetes mellitus* the glycogen content of most of the tissues is found to be decreased, although for some reason the cells of part of the convoluted tubules of the kidney, the heart muscle and the leucocytes become loaded with it," remarking also, "no explanation for this is known."

Although we are dealing with a manifestation of hyperadrenalism, the usual symptoms and histological changes of this condition: bulimia, arteriosclerosis, high blood tension, etc., are few. This is because they are submerged by the symptoms of pancreatic exhaustion, the organ showing lesions such as interacinar pancreatitis with sclerosis or degeneration of islands of Langerhans, as in 79 out of 90 cases examined by Cecil,[113] the remaining 11 showed either diminution of the islands or atrophy of the organ as a whole. Weichselbaum[114] also found the islands of Langerhans "strikingly pathologic," 183 cadavers of diabetes, although no such lesions were found in the pancreas of 73 in which death had been due to tuberculosis. The importance of the pancreas, *i.e.*, its trypsin, in the very life of the tissue cell and in the defensive functions of the entire organism explains the severity of the complications that ensue when the pancreatic lesions are widespread. Particularly is this the case when acidosis (acetonemia) prevails, the trypsic enzyme requiring an alkaline medium.

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[112] W. G. MacCallum: Text-book of Pathology, Phila. and London, 2d ed., 105, 1920.

[113] R. I. Cecil: Jour. Exper. Med., xi, 266, 1909.

[114] A. Weichselbaum: Wiener klin. Woch., xxiv, 153, 1911.

The gravity of the pancreatic lesions is due to the fact pointed out by Lépine[115] that the pancreas has the highest temperature of the body during digestion. When we recall the influence of high temperature on the proteolytic activity of trypsin, the fact that autolytic lesions followed by sclerosis are found in the organ need not excite surprise. They sometimes involve the entire pancreas.

Diabetes is inadequately described in the average text-book, therefore, as "a disorder of metabolism characterized by impairment of the ability of the tissues to utilize carbohydrate." The tissues are only impaired as the result of a primary disorder of the adreno-pancreatico-hepatic mechanism. The symptoms of the disease, considered from this viewpoint, assume a different aspect—one enabling us to identify their source, and therefore to direct our therapeutic efforts more intelligently.

Due mainly to hyperadrenia and the resulting constriction of the arterioles at large plus the excessive loss of fluid caused by the polyuria, are the initial thirst, dryness and redness of the oral cavity and tongue, and the viscidity of the saliva, the dry and harsh skin with deficient perspiration and epithelial dryness of the mucous membranes, which in turn entails pruritus, and the excessive appetite due to accelerated tissue metabolism, with tendency to emaciation and irritability. This constitutes the *sthenic phase.*

Then appear, increasingly, phenomena which coincide with the presence of more or less marked serious lesions in the pancreas, the result of excessive metabolism therein and perhaps of autolysis. Its secretory activity becoming impaired the tissue cells of the body at large begin to miss the ferment without which, as Vaughan said, we have seen, a cell "is already dead whatever be the kind or amount of pabulum surrounding it." This initiates the *asthenic phase,* manifested by pallor, sometimes with obesity, or emaciation and debility. Denutrition following, the teeth become carious and tend to fall out; various so-called complications follow, neuritis and other nervous disorders, with loss of reflexes, gastrointestinal disturbances. boils, carbuncles, necrotic or gangrenous foci, disorders of vision through atrophy of the optic nerve, cataract, impotence. sterility, etc., and other familiar complications. Among these is hypothermia which, when persistent, indicates another pathological development, exhaustion of the adrenals, so marked in some instances as to cause bronzing similar to that observed in Addison's disease. Acidosis, giving the breath a peculiar odor of apples, due to defective consumption of fats, is a threatening symptom which a too rigorous diet may promote. The patient is then liable to various infections, tuberculosis, pneumonia, otitis media, cutaneous disorders, etc. The acute infections are always serious in this advanced stage, the deficiency of trypsin, the main defensive ferment and concomitant failure of the adrenals and thyroid, practically annulling the production of autoprotective substances. In about one-half of the cases death is due to coma, the result in turn of acidosis and failure of the defensive mechanism to antagonize it.

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[115] R. Lépine: Arch. de Méd. Exper., xi, 743, 1899.

The treatment under present conditions only aims to control the symptoms. While many patients are greatly improved, particularly since the Allen treatment has been added to our resources, the fact remains that if the initial pathogenic factors could be eliminated, which at present is not even attempted, hope for better results might be entertained. This should include, besides the dietetic régime, a careful search for the cause of the hyperadrenia of which overeating, a familiar cause of diabetes and hyperadrenalism, is a prominent example. From my viewpoint the Allen treatment is helpful also owing to the fact that temporary starvation reduces the adrenal erethism. During the world war and after, various authors including Magnus-Levy,[116] Elias and Singer,[117] and others, emphasized the marked reduction of mortality from diabetes which they attribute to cessation of overeating in Germany and of rationing in Austria. Allen[118] also found that even in those patients who become free from glycosuria on the withdrawal of sugar only, other foods should also be limited. Meats are active adrenal stimulants; in my experience wheat flour seemed also somewhat so. The beneficial influence of fast days and half days is likewise partly due to inhibition of the adrenals, while the familiar harmful effects of violent exertion, are accounted for by its exciting effect upon these organs and the resulting exaggerated oxygenation and metabolism, which in turn underlie the pancreatic lesions.

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[116] A. Magnus-Levy: Deut. med. Woch., xlv, 1379, 1919.
[117] Elias and Singer: Wiener klin. Woch., xxxii, 508, 1919.
[118] F. M. Allen: Jour. Exper. Med., xxxi, 363, 1920.

Any other etiological factor should, if possible, be removed. All those enumerated in text-books, including fright, violent excitement, head trauma, etc., tend to cause hyperadrenia.

In 1905[119] and repeatedly since, I urged on the basis of concurring histological, physiological and clinical data, that the glycosuria due to lesions of the pituitary was produced *through the intermediary of nerve-paths* passing by way of the infundibulum basal tissues, medulla, spinal cord and the splanchnic nerve to the adrenals.. This also has been confirmed. · Keeton and Becht,[120] after an experimental study (1919), state that "the data presented demonstrate clearly that if the stimulus be prevented from reaching the level of the adrenals, no hyperglycemia results. from stimulation of the hypophysis." Much additional evidence of the presence of a nerve path along the basal tissues will be submitted later.

How subdue the adrenal erethism while and after eliminating its cause? This question emphasizes the danger of the prevailing promiscuous use of organic products and accounts for the harmful effects recorded by some observers, particularly with hypophysis sicca, which owes its activity in part to the chromaffin substance it contains. Strychnine, an adrenal stimulant, is also harmful at this stage. Conversely, the use of arsenic, preferably the bromide of arsenic (Clemens's solution) the dosage of which is one-third that of Fowler's, to inhibit the thyroid and thereby general metabolism in both the adrenals and pancreas; strontium bromide, to depress the sensory centers; chloral hydrate, for the same purpose when there is insomnia; the coal-tars, salicylates, etc. The use of considerable fluid, alkaline waters preferably Vichy (Source Célestin), saline proctoclysis or even hypodermoclysis, are also indicated during the sthenic stage to decrease the viscidity of the blood and promote osmosis. All these agents added to the dietetic measures—including enough carbohydrate to control the acidosis—are not only effective, but tend greatly to arrest the pancreatic morbid process. When we realize that in keeping with all endocrins, a fraction of the pancreas can carry on its functions—a fact emphasized by the protective effect of the experimental graft—the feasibility of such a result suggests itself.

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[119] C. E. de M. Sajous: Jour. Amer. Med. Assoc., xliv, 364, 1905.
[120] Keeton and Becht: Amer. Jour. Physiol., xlix, 248, 1919.

The presence of the asthenic phase symptoms indicates the need of compensative treatment especially when dyspnea, hypothermia and low blood pressure are present. Then the hypophysis sicca, in 1/10-grain doses thrice daily during meals, is to be preferred to adrenalin, its effects corresponding with those of the adrenal cortex and medulla. Koopman's experience[121] corresponds with mine. It often increases markedly the protein-, bread-, and meat- tolerance. Concomitantly, however, pancreas or better pancreatin, should be given in full doses, one hour after meals.

Diabetes Insipidus.—In this disorder, characterized by marked polyuria, urine of low specific gravity and excessive thirst, "the true nature of which is unknown," according to Elsner,[122] the essential factor from my viewpoint is hypoadrenia. It may be caused by severing the splanchnic nerve which contains the secretory nerves to the adrenals, as shown by Lépine,[123] and may be checked by vasoconstrictors especially those giving adrenal reactions such as posterior pituitary gland, or which stimulate the adrenals, such as strychnine, or direct vasoconstrictors of the ergot type.

Lépine's observation that section of the splanchnic nerves arrests polyuria coincides with Keeton and Becht's arrest of glycosuria by the same operation referred to. But in the former observer's experiment, polyuria was *produced* in normal animals by section of the splanchnic, while in Keeton and Becht's, glycosuria was *arrested* by the same procedure. Hence my conclusion that polyuria is due, not to stimulation of the adrenals as in diabetes, but to arrest of the normal nervous impulses from the posterior pituitary to that organ. Recalling in this connection that in 1907[124] I traced this path "through nerves from the giant-cell suprainfundibular nucleus and in the tuber cinereum," the following conclusion of Camus and Roussy[125] is of special interest: "The important fact is that a superficial lesion of the *base* of the brain, often involving only the surface and produced involuntarily in the removal of the pituitary body, is followed by polyuria. In our animals it seems that the opto-peduncular region alone marks the zone within which a lesion is followed by polyuria. It lies at the level of the grey substance of the *tuber cinereum* in the vicinity of the infundibulum."

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[121] J. Koopman: Endocrinology, iii, 485, 1919.

[122] H. I. Elsner: Monographic Medicine, N. Y. and London, vi, 1122, 1916.

[123] R. Lépine: Sajous's Analytic Cyclopedia of Practical Medicine, Phila., ii, 484, 1899.

Besides the diuresis, there are other signs of dilation of the arterioles, due to the hypoadrenia: Abnormal flow of saliva, relaxation of the muscular coat of the stomach causing digestive disorder, constipation also due to muscular atony, reduction of the oxygen intake and of the carbon dioxide output, deficient cutaneous perspiration with dryness of the skin. All these symptoms, in true cases of diabetes insipidus are promptly relieved and often cured (unless due to cerebral or pituitary tumors or other organic disorders which impair the conductivity of impulses to the adrenals) by administering hypophysis sicca in 1/10-grain doses with ergotine, 1 grain, both three times daily, to compensate for the adrenal insufficiency and the resulting relaxation of the arterioles including those of the hypophysis and kidneys. In most cases, only the hypodermic use of posterior pituitary liquid will prove efficient. Anterior lobe, as observed by Motzfeldt[126] has no such effect.

HEPATIC DISORDERS.—Although *portal cirrhosis* is usually associated with the excessive use of alcohol, it likewise occurs, as is well known, in people who never indulge in it, the Brahmins for instance. They use, however, irritating condiments, red pepper, ginger, cardamon, etc., very freely. Various poisonous materials circulating in the blood may also cause it, as emphasized by W. G. MacCallum,[127] while diseases, syphilis, tuberculosis and malaria, for instance, and various pathogenic organisms are also familiar causes. And yet the typical lesions produced in the hepatic lobule are similar in all, the destructive process, beginning with the central cells, leading finally to the connective tissue formation which, by contracting, gives the cut surface its familiar "hobnail" appearance.

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[124] C. E. de M. Sajous: Internal Secretions and the Principles of Medicine, ii, 982, 1907.

[125] Camus and Roussy: Endocrinology, iv, 507, 1920.

[126] K. Motzfeldt: Boston Med. and Surg. Jour., clxxiv, 644, 1916.

The marked disintoxicating function of the liver explains the uniformity in the character and progress of the lesions produced, but this in itself bespeaks a corresponding uniformity in the manner in which they are brought about. In other words, a single more or less active antitoxic process, intense in proportion with the degree of toxicity to be met appears to prevail for all. In his original experiments Opie[128] found that while chloroform, whether fed or given by inhalation to his animals, caused a temporary necrosis in the hepatic lobule, the concomitant administration of small doses of phosphorus or inoculations with streptococci or colon bacilli gave rise to the destructive form followed by fibroid overgrowth. He concluded, therefore, that these bacteria which, in the normal liver, produce no lesions, induced the typical form of cirrhosis when the vitality of the liver-cells had been depressed by chloroform. From my viewpoint, however, the necrosis caused by the chloroform, even though recovered from, can hardly be regarded as a mere depression of activity; it is an active lesion which the phosphorus or bacteria have aggravated sufficiently to render permanent by increasing the activity of the local defensive and proteolytic process, *i.e.*, a true digestive necrosis.

The nature of the process suggests itself when we recall that the pancreas is simultaneously diseased, and often correspondingly so. Thus Lando[129] out of fifteen cases of hepatic cirrhosis found that while all showed overgrowth of connective tissue, in twelve of these the overgrowth about corresponded with that of the liver. D'Amato,[130] in a comprehensive study, noted besides the cirrhotic lesions, hyperemia, hæmorrhagic infarcts and diffuse necrosis, and attributed to the pancreatic lesions the occurrence of diabetes in hepatic cirrhosis. Klippel and Lefas also describe eight cases to "illustrate," they state, "the bond that unites the pathology of the liver to that of the pancreas." This bond I attribute to the excessive activity of the pancreas, rendered necessary by the abnormal need of trypsin, to meet the requirements of the disintoxicating process in the liver. In an experimental and clinical study Fischler[131] found that when more than the normal proportion of trypsin gets into the blood—as observed after Eck fistulas—necrosis of the central liver cells follows. When it occurs with chloroform, he declares "it is merely the last straw rendering manifest the injurious effect of trypsin on the parenchyma of the liver."

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[127] W. G. MacCallum: Jour. Amer. Med. Assoc., xlvii, 984, 1906.
[128] E. L. Opie: Trans. Assoc. Amer. Phys., Phila., xxv, 140, 1910.
[129] D. H. Lando: Zeit. f. Heilkunde, xxvii, Abtheil. f. path. Anat., 1, 1906.
[130] L. D'Amato: La Riforma Medica, xix, 981, 1013, 1903.

Briefly, from my viewpoint, the "defensive ferment" trypsin being needed to satisfy the needs of the disintoxicating process in the liver, the pancreas is itself stimulated abnormally and becomes the seat of lesions. The excess of trypsin, carried to the liver by leucocytes, which cells are well known to contain it, finds therein a high temperature ranging around 105° F., which, as we have seen, increases the activity of enzymes, and an active autolysis is initiated which leads finally to the cirrhotic process, the many symptoms of which are mainly those of hepatic obstruction.

Personal experience has shown that drugs are more harmful than useful, since they merely impose upon the liver additional sources of functional activity. A bread and water, or bread and milk diet for a few days, followed by a bland régime and the copious use of pure water with complete rest, do far more than vaunted drugs, provided the causative habit is abandoned. When ascites occurs, as we have seen, a valuable resource is adrenalin.

All this but exemplifies, with few variations, the underlying process of many morbid conditions, not only in the liver itself, such as *acute yellow atrophy, amyloid liver,* etc., but also in other organs, the lungs, kidneys, spleen, brain and spinal cord for instance, particularly when infection is the exciting factor.

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[131] F. Fischler: Mitteil. a. d. Grenzgeb. der Med. u. Chir., Jena, xxvi, 553, 1912.

The foregoing examples, which readily introduce over thirty diseases, sufficiently emphasize the soundness of the opinion first expressed nearly two decades ago in the present work that the endocrins dominated all bodily activities, their pathology and treatment, and that they would place our conception of disease on a more scientific footing.

CHAPTER II.

THE FUNCTIONS AND DISEASES OF THE ADRENALS.

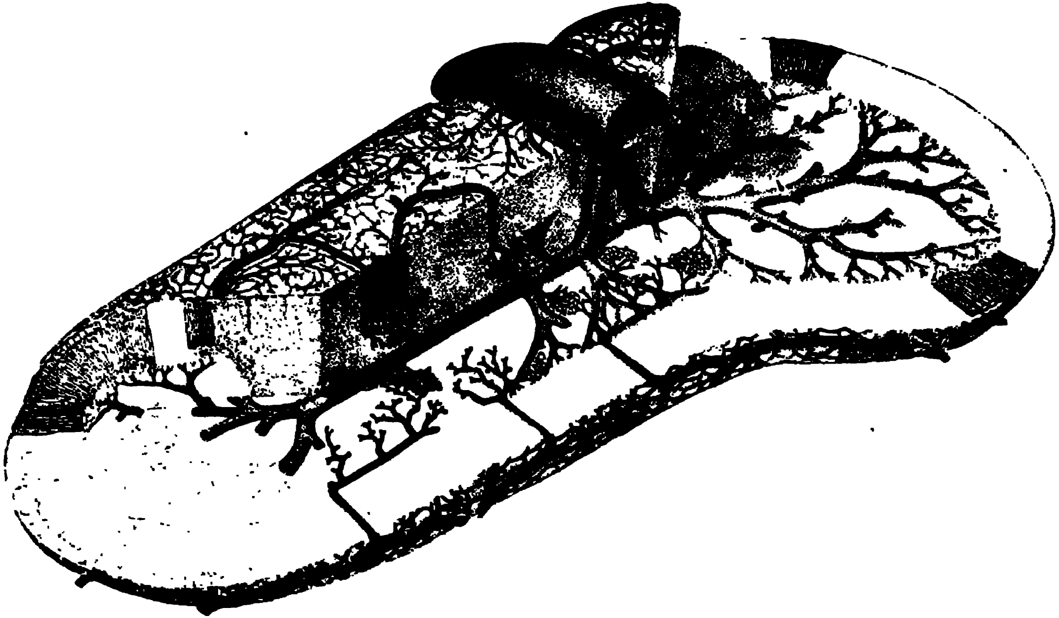
STRUCTURE OF THE ADRENALS AND THE CHROMAFFIN SYSTEM.

A FEATURE of paramount importance whenever the physiological functions of the adrenals or any pathological condition of which they may be the seat are studied, is that these organs are but the major structures of a vast system, which has been termed the "chromaffin system" because a solution of potassium bichromate stains brown a substance they contain which corresponds with the medulla of the adrenals. This phenomenon, first observed by Henle in 1865, has since been noted by other observers to apply to the sympathetic nervous system and its ganglia, the carotid glands and other structures, including the posterior lobe of the pituitary body. Wherever obtained therefore, this chromaffin reaction indicates the presence of adrenal medulla cells. The power of adrenalin production is therefore not limited to the adrenals, the major organs of the system.

Another feature of importance is the presence in the adrenals of two different types formed independently and originating from different sources, the cortex and the medulla. (See colored plate opposite page 46.) Whereas the cortex or outer portion of the adrenals, the cells of which contain lipoid (fat-like) substances, develops, in the embryo, from the "intermediate cell mass," or that portion of the mesoblast from which the mesonephros or primitive kidney is formed, the medulla or inner portion, which alone gives the chromaffin reaction, is produced by outgrowth *from the sympathetic system,* and is considered as consisting of profoundly changed nerve-cells. Even on naked-eye examination the division of the adrenals into two distinct segments differing in both color and consistency is striking. These two types of tissue exist in all vertebrates, but in mammals alone are they combined as a definite cortex and medulla separated by a clearly marked and continuous dividing line. In birds the two varieties of cells are intimately interwoven in one common tissue mass. In some reptiles, including snakes and lizards, separate groups of medullary cells are dispersed in the cortex, especially its ventral portion, while in others, such as the tortoise, the condition is analogous to that found in birds. In many amphibia, including the frog, the adrenals are seen as thin, linear, yellow organs in contact externally with the likewise elongated but more massive kidneys, while in other amphibia, such as the salamander, they are portioned off into small isolated masses, similarly in contact with the kidneys. The amphibian adrenals, like those of the higher verterbrates, contain aggregations of both lipoid-containing and chromaffin cells, the latter lying not in the interior of, but on the outside of, the former.

Vertebrates lower in the phylogenetic scale than the amphibia differ from all the others in exhibiting complete anatomical independence of the lipoid and chromaffin tissues. The former tissues constitute what is termed the interrenal body, while the latter compose what may be properly termed the adrenal or adrenalin-forming organs. In fishes the interrenal cells exhibit constantly a vesicular or tubular arrangement. In the selachian fishes the interrenal body is a homogeneous organ situated between the caudal termination of the kidneys; in the ganoids there are interrenal "corpuscles" disseminated in the interior of the kidneys, while in the cyclostomata, or eel-like fishes, the interrenal tissues occur as small cell groups extending from the head kidney along the animal's long, slender body to the tail and affixed to the posterior cardinal veins.

Wholly separate from the interrenal tissues in fishes are the chromaffin or adrenal organs, which, in the selachians, lie in proximity to the sympathetic ganglia, between the kidneys and the dorsal parietes in the caudal or tail portion of the animal's body. In the teleosts and the ganoid fishes, the adrenal organs lie actually in the walls of the cardinal veins, and in the cyclostomata they occur as band-like masses of tissue, interposed between the cardinal veins and the aorta. This unfailingly suggests the arrangement met with in mammals, in which the ad-



CIRCULATION OF THE ADRENALS IN THE DOG. [J. M. Flint.]

[Johns Hopkins Hospital Reports.]

renals lie in close proximity to the inferior vena cava, into which their secretory product, adrenalin, is almost directly poured.

The essential difference between the interrenal and adrenal tissues appears still further when their embryological sources are inquired into. The interrenal cells are derived, in the embryo, from the mesoderm or primitive middle layer of tissue-cells. The organs they are destined later to constitute first appear as bud-like cellular elevations from the peritoneum, at a time when the sexual glands are likewise beginning to develop. Gradually assuming the appearance of definite, separate organs, the resulting tissues, already consisting of cells of characteristic interrenal type, migrate through the connective tissues to different situations, then undergo more or less complete degeneration and absorption at the cephalic or head end of the body and coalesce to form large interrenal glands at the caudal end.

The adrenal or chromaffin tissues, derived from the primitive ectoderm or outer cell layer of the young embryo, develop in close conjunction with the sympathetic nervous system. In the formation of the sympathetic ganglia, a part of the primordial tissue (*anlage*), instead of forming primitive nerve-cells, becomes set apart as the seat of origin of the subsequent chromaffin cells. So intimately are the two sorts of tissue originally blended that the chromaffin cells may remain either individually or in groups of less or greater size directly imbedded in the midst of the nerve elements. This, where it persists, represents the most primitive permanent relationship of chromaffin to sympathetic tissues. In the selachian fishes, however, the two tissues do not remain so intimately united. The chromaffin cells either collect together in a large group which remains at some point within the ganglion or leaves it to form a definite external mass which, nevertheless, always remains in the immediate vicinity of the ganglion. In the amphibia and higher vertebrates, a further step in the separation of the two forms of tissue takes place, the chromaffin cell groups in part leaving the sympathetic completely and exhibiting no feature suggestive of a common origin with it. Even here, however, minor portions of the chromaffin tissue remain within or in close apposition to the sympathetic structures.

Coalescence of the interrenal and chromaffin tissues takes place first in the amphibia, and constitutes the last stage in the embryologic transmigrations to which they are subject. Thus, in amphibia, small masses of chromaffin cells, instead of remaining with the sympathetic ganglia, pass in an anterior and mesial direction to the interrenal bodies, with which they unite and become more or less intermingled. In the human embryo, when five weeks old, an analogous process takes place. Primordial sympathetic cells begin to migrate from the larger sympathetic group in the abdomen to the interrenal tissues, already aggregated in the form of definite organs, make an entrance through the capsules of the interrenal bodies, and become imbedded among the columnar and other cell groupings of the latter. The migration of sympathetic cells continues throughout fetal life. For a time the imbedded sympathetic cells remain in their primitive state. Only in the beginning of the fourth month, in the human embryo, is their chromaffin property developed. In birds, as already mentioned, the chromaffin tissue remains throughout interwoven with the interrenal cells. In mammals the interrenal tissue finally becomes definitely segregated as the cortex of the adrenals and the chromaffin tissue as their medulla.

HISTOLOGY OF THE ADRENALS.—The adrenal *medulla* in man consists of a loose network of columnar or rounded masses of cells situated in close contact with the blood-vessels. As a rule, the adrenal cells are separated from the lumina of the capillaries or venules by an endothelial cell membrane, though in some localities a thin sheath of connective tissue is interposed. No cavities exist between the cells forming part of individual columns or other groups, *i.e.*, there is no acinar arrangement. The columns are radially disposed around the large central vein of the adrenal, into which the secretory product or products of the gland are discharged.

The true medullary cells, for the most part, are polyhedral in form, and are separated only by a very thin cementing layer. Their nuclei, eccentrically situated (at the opposite side of the cell from the adjoining vascular channel) are poor in chromatin and present a vacuolar appearance. They are circular or oval in shape. The surrounding protoplasm in these cells, presenting a hyaline, highly refractile appearance in unstained specimens, nonetheless harbors numerous very fine granulations, sometimes closely packed together, at others sparsely distributed. After fixation with alcohol or formalin these cells present a paler appearance, upon staining, than do those of the adrenal cortex. The granules just referred to are of great interest in that they impart to the cells containing them their chromaffin property. They are soluble in water and in alcohol, but insoluble in ether, xylol, and glacial acetic acid. In unfixed preparations they can be made visible, though rather indistinctly at best, with iron hematoxylin. After fixation with Zenker's fluid, on the other hand, they can be stained fairly well, as a rule, with eosin. The granules are to a certain degree related, according to Biedl,[89] to nuclear coloring material. They are stained violet by a mixture of methylene blue and eosin, and pale pink by Ziehl's solution. The chromaffin property at once strikes the observer when a fixing solution, such as formalin, to which a salt of chromic acid has been added, is employed. A color varying from yellow to brown is at once imparted to the adrenal medulla as a whole. Some cells, however, are stained much less intensely than others, and even in individual cells the granules do not stain evenly. A peculiarity of this chromaffin property is that it is lost in a relatively short period of time after death; after twelve to, at most, thirty hours have elapsed, attempts to secure the brownish coloration completely fail. Once the brown color has been produced, on the other hand, it cannot be removed by washing with water. Another, less striking but classic reaction characteristic of the adrenal medulla is that of Vulpian, who, we have seen, noticed that upon application of a solution of ferric chloride, the cells of the medulla develop a green color.

The mechanism of epinephrin secretion in the medullary cells is described by Stoerk and von Haberer[90] as follows: The chromaffin substance produced in the granules progressively augments up to a certain limit, when it begins to diffuse into the cytoplasm between the granules and even, sometimes, into the nucleus. When the entire cell has thus become sufficiently impregnated with the chromaffin substance, further diffusion takes place out of the cell into the blood of the neighboring small vascular channel. A rather complete discharge of the product is thus effected, the cell as a result temporarily losing its chromaffin property. In the adrenal venules the chromaffin substance appears as a mucoid material, colored yellowish brown and characteristically refractile, which passes down into the main adrenal vein and thence enters the general circulation in the interior vena cava. Small, brightly shining bodies, apparently distinct from the mucoid masses, have been noticed imbedded in the latter, and were formerly thought alone to represent the true secretion of the adrenals. Stoerk and von Haberer have shown that these bodies are, indeed, not identical with the surrounding mucoid material. No definite conception has as yet been formed, however, of their functional significance. The same is true of the large, rodlike, and wedge-shaped granules demonstrated in the cytoplasm of the cells of the medulla by the same investigators, who found them stained black when iron hematoxylin was used. Lipoid and pigment bodies, of unknown significance, have also been noticed in these medullary cells.

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[89] Biedl: Innere Sekretion, vol. I, p. 343, 1913.

[90] Stoerk and von Haberer: Archiv für mikroskopische Anatomie, No. 72, S. 481, 1908.

The *cortex* of the adrenals, which incloses the medulla on all its aspects, is a broad mass of tissue itself surrounded by a connective-tissue capsule which, at intervals, gives off radially disposed partitions extending down through the gland-tissue, and there progressively dwindling until so thin as to be hardly perceptible. These partitions themselves are joined, at a certain distance from the external capsule, by a fresh series of cross partitions, which form the inner limit of the outer or glomerular zone of the cortex. Proceeding farther inward from the periphery two additional zones, the fascicular and the reticular, respectively, are met with, the former relatively broad and the latter narrower, like the glomerular zones. More pronounced in some of the lower animals than in man, this division of the cortex into zones entails no fundamental difference between the cells constituting the several layers. In the glomerular zone the connective-tissue trabeculæ are so directed as to inclose spherical or oval groups of the columnar epithelial cells. In the broad fascicular zone, on the other hand, they run for the most part in a radial direction, marking off parallel columns of epithelium, joined together only occasionally by oblique or transverse columns or connective-tissue strands inclosing capillary vessels. In the innermost or reticular zone, the connective-tissue strands have become distinctly attenuated, and inclose thinner cords of cells than exist in the middle zone, these cords, moreover, so anastomosing with one another as to form a coarse, irregular reticulum. The cells differ somewhat in size and shape in the several zones of the cortex. In the outer zone they are relatively small and of varying outline; in the middle zone, considerably larger, rounded, polygonal, or elongated, and in the inner zone, again smaller, and cubical or polygonal in outline. As in the medulla, the cortical epithelia lie in close relationship to blood-vessels, from the lumen of which they are separated solely by the endothelium of the vessels themselves, and occasionally, in addition, a thin layer of connective tissue.

Of firmer consistency than the medulla, the cortex of the adrenals presents, in contrast to the reddish vascular appearance of the latter, a yellowish tint, due to the extensive content of lipoid granules which characterize its epithelial cells. The granules ordinarily measure one to four microns in diameter, though occasionally they coalesce to form larger droplets—a condition which can be promoted by subjection of the tissues to strong acids or to potassium hydrate. Upon fixing adrenal tissue with formalin, sectioning with the freezing microtome, and staining with the ordinary fat stains, scarlet R or sudan III, the granules will be found to assume a red color. If osmic acid be used, however, the lipoid granules will not, like ordinary fats, be at once stained black, but will take on at first only a brown color, and become black only if later subjected to the action of alcohol. When thus prepared, the granules become insoluble in chloroform and benzol, but they remain soluble in ether and in xylol, which cannot, therefore, be used in the further treatment of the tissue specimen without causing their disappearance. Like other fatty substances, the adrenal lipoid is not stained by methylene blue or fuchsin stains. There are found, however, in the cells of the adrenal cortex other granules which do become stained in fuchsin—"Altmann's fuchsinophile granules." A special study of these has been made by Plecnik.[91]

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[91] Plecnik: Archiv für mikroskopische Anatomie, No. 60, S. 414, 1902.

who found them well marked even in the adrenals of embryos. For the most part of the same size as the lipoid granules, they occur most thickly in portions of the epithelial cells where the latter are most sparsely distributed, and exhibit a tendency to diminution in size as the nucleus is approached. A certain proportion of them disappears in common with the lipoid granules when the tissues are moistened with ether. No evidence that these granules can become converted into lipoid granules has been found, and their exact significance is unknown. The third and last type of minute inclosed bodies found in the cortical cells is that of the pigment granules, which occur, in particular, in the reticular or innermost zone. These remain behind when cells the lipoid bodies of which have been stained with osmic acid are treated with ether and iron hematoxylin, differentiation between the lipoid granules and the pigment bodies—the latter naturally yellow but now stained black by the iron hematoxylin—being thus effected in a striking manner.

The exact chemical nature of the doubly refractive substance present in the lipoid granules of the adrenal cortex has been the subject of repeated investigation and discussion. Aschoff's[92] view, supported by the chemical researches of Biedl, is that it is made up of cholesterin esters. This is the prevailing view. The functional significance of these cholesterin bodies, as well as of the cortical tissue as a whole, has given rise to much discussion, as yet with but little result. There is no evidence that the lipoids are discharged into the blood-stream as a secretion by the cortex. *In vitro* the cortical lipoids have been found capable of fixing and neutralizing toxins, and Bonamour[93] has advanced the theory that the cortex has for its purpose to absorb and neutralize toxic metabolic products. No demonstrative evidence to this effect has, however, been forthcoming. Biedl,[94] on the other hand, believes there is sufficient evidence to warrant consideration of the interrenal system as a true internally secreting organ, to be included in the group of organs which, like the thyroid, thymus, pituitary, and sexual glands, produce assimilatory hormones exerting an influence, directly or indirectly, upon general somatic and psychic development. This evidence consists of the observations pointing to the influence of the adrenal cortex on the development of the brain and sexual glands, upon body growth, and upon the changes taking place in the period of puberty.

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[92] Aschoff: Ziegler's Beiträge zur allgemeine Pathologie und pathologischen Anatomie, S. 47, 1909.

[93] Bonamour: Thèse de Lyon, 1905.

[94] Biedl: Internal Secretory Organs, p. 292, 1913.

The close anatomical relationship between the chief interrenal and true adrenal tissues has naturally given rise to speculation as to a possible functional relationship between them. The fact that the adrenal tissues lie, from the circulatory standpoint, immediately distal to the interrenal tissues, blood which has just circulated through the latter, passing into the former immediately after, suggests that the adrenal cortex supplies the medulla some material of value in the secretory process of the latter. As Mulon[95] points out, however, no such material is known, and the anatomical union of the tissues, while possibly advantageous, is not an absolute necessity, since there are many vertebrates in which the two tissues are some distance apart. Experiments purporting to show the presence of adrenalin in the adrenal cortex have been proven technically faulty. Voegtlin and Macht,[96] on the other hand, have detected in the cortex a body having a digitalis-like action and Iscovesco[97] also demonstrated in it a lipoid exerting a tonic effect on the heart. Langlois[98] has advanced the theory that the cortex chemically transforms the poisonous wastes arising in the metabolism of contracting muscular tissue and thereby prepares a substance from which the medulla elaborates adrenalin.

The *blood-supply* of the adrenals is extensive and is derived, as is well known, from no less than three sets of suprarenal arteries. The arterial trunks entering the capsule of the gland undergo, for the most part, an immediate division into small vessels which, after forming a network of capillaries to supply the capsule itself, pass inward in the connective-tissue septa and trabeculæ to supply each zone of the cortex, forming in each a capillary network which corresponds with the arrangement of the connective tissue therein. After circulating through the entire cortex the blood passes into broad, sinus-like spaces in the medulla which are in intimate relationship to the chromaffin cells. From these it passes into narrower venules and thence into the central adrenal vein or veins. The medulla receives blood in addition from the "perforating arteries" of Srdinko,[99] which pass directly through the cortex from the capsule, without subdivision. This blood likewise is eventually discharged into the adrenal vein.

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[95] Mulon: Paris médical, July 19, 1913.

[96] Voegtlin and Macht: Journal of the American Medical Association, Dec. 13, 1913.

[97] Iscovesco: Bulletins et Mémoires de la Société médicale des Hôpitaux de Paris, Dec. 26, 1912.

[98] Langlois: Quoted by Mulon, *loc. cit.*

But little is known as to the precise distribution of the *lymphatics* in the adrenals. In a general way, the lymphatics follow the course of the blood-channels. Small aggregations of lymphocytes have been found in the connective-tissue stroma of the adrenals, likewise at times eosinophile leucocytes. Of special interest and possible significance are the elastic and smooth muscle-fibers also described in this tissue. According to Dewitzky[100] there exists in the adrenal medulla a network of elastic tissue having for its special purpose to hold the blood-vessels open.

The *nerve-supply* of the adrenals is very rich, even more in the medullary than in the cortex. In the capsule are to be found plexuses of non-medullated and, less abundantly, medullated fibers, connected with groups of sympathetic ganglion cells. Fine fibers pass from the capsular plexuses along the connective-tissue septa of the cortex into relationship with the columns of cortical cells, and terminate in elongated thickenings at the surface—not in the interior—of these columns. Through the cortex also pass larger and more numerous nerve-bundles destined for the tissues of the medulla, where they form a rich plexus the ramifications of which extend among the chromaffin cells and form arborizations around them. According to Dogiel,[101] to whom we are indebted for the most complete study of the adrenal nerve-supply extant, the nerve-fibers can be followed up to the venous walls themselves in the case of cells adjoining such veins. In relation with the plexuses of the medulla, and less abundantly with those of the cortex, are also to be found groups of sympathetic ganglion cells. Variable in size, these groups occur either along the nerve-trunks, at the boundary between the medulla and the cortex or, occasionally, in the fascicular zone of the cortex. These ganglion cells give off neurites and dentrites which form arborizations in the vicinity of other ganglion cells, but do not come into relationship with the parenchyma cells of the medulla themselves.

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[99] Srdinko: Sitzungsberichte der böhmischen Kaiser-Franz-Joseph-Akademie. Prag, Nos. 12, 16, 28, 1905.

[100] Dewitzky: Ziegler's Beiträge, No. 52, S. 435, 1912.

[101] Dogiel: Archiv für Anatomie und Physiologie, S. 90-104, 1894.

SUBSIDIARY ADRENAL AND INTERRENAL TISSUES.—The widespread distribution of both adrenal and interrenal tissues in the embryo and in adults of the lower animal forms in which these tissues exist finds expression in the adult mammalian animal in the presence of small, outlying masses of these tissues, entirely separate from the medulla and cortex of the adrenals. Of especial interest are the subsidiary chromaffin organs, grouped in conjunction with the medullæ of the adrenals under the term "paraganglia." These include, in particular, the carotid glands, the tympanic glands, and the parasympathetic organ of Zuckerkandl, situated in front of the bifurcation of the abdominal aorta.

The *carotid glands,* each of about the size of a grain of rice, lie in or near the crotch of the bifurcation of the common carotid arteries. Originally considered chiefly as vascular or glomerular structures, the true nature of the organs was discovered, as already mentioned, in 1892 by Stilling, who demonstrated the chromaffin property of the epithelium they contain. The cells are large and polyhedral, arranged in spheroidal groups, with very thin intervening cell-walls, and in close apposition to large, thin-walled capillaries, in which the narrow columns of epithelial cells are freely bathed. The source of the glands is in the embryonal ganglion cells of the intercarotid sympathetic nerve-plexus. The vascular and connective tissues of the glands augment with age, the epithelial cells, on the other hand, undergoing a corresponding diminution. As a rule, only a small proportion of the epithelial cells of the carotid glands are colored brown by chromium salts. This has been found to apply also to the epithelial tumors occasionally met with in these organs. At least two observers have even denied them, on the basis of personal experiments, any chromaffin property whatever, and expressed the opinion that these organs should no longer be grouped among the "paraganglia." At all events, their importance as components of the chromaffin system would appear to be, at best, slight.

[NOTE.—The *coccygeal body*, first studied by Luschka in 1859 (Virchow's Archiv, B. 18) is a reddish-yellow organ of about the size of a small pea, situated in front of the apex of the coccyx. Though provisionally classed by this observer among the ductless glands, and since frequently compared, by reason of its structural peculiarities, with the carotid glands, pituitary body, and adrenals, the coccygeal body was shown by Stoerk in 1907 (Archiv f. mikrosc. Anat., B. 69) to present no chromaffin property, either in fetal or in extra-uterine life, and to be devoid of any relationship, from the developmental standpoint, with the sympathetic system. Recent embryological studies seem to have shown that the coccygeal body arises as a local thickening of the walls of the median sacral artery, with subsequent formation of an arteriovenous anastomosis and the production of a network of twisted blood-vessels. The earlier conception of the coccygeal body as a ductless gland has thus been abandoned.]

The *tympanic glands* are small groups of chromaffin cells situated in apposition to the nerve of Jacobson in the tympanic canal on either side of the body.

The most important subsidiary mass of chromaffin tissue is that constituting the *organ of Zuckerkandl,* which represents the lower, independent extremity of a large, elongated chromaffin body extending in the embryo from the level of the main adrenal bodies to the bifurcation of the aorta. In the newborn mammal the upper portion of this elongated body is, moreover, represented by a number of smaller chromaffin groups disseminated in the intervening space. Such groups have also been met with below the organ of Zuckerkandl, in the angle formed by the iliac arteries and on the lateral aspects of the rectum. The common embryological origin of the sympathetic nervous tissue and the chromaffin organs is even more strikingly shown in the fact that collections of chromaffin cells may be found imbedded in sympathetic nerve-ganglia, wherever the latter may be situated. Such collections have been frequently noted, for example, in the left stellate ganglion (Wiesel), and in various peripheral sympathetic ganglia, such as those of the celiac, abdominal aortic, inferior mesenteric, and superior and inferior hypogastric plexuses. Wiesel[102] (quoted by Biedl[103]) found a paraganglion 10 to 15 millimeters long at the root of the left coronary artery in a human heart. Other relatively uncommon sites noted have been the point of entrance of the superior vena cava into the heart, the pulmonary artery, the root of the superior mesenteric artery, the intestinal wall, the abdominal nerve-plexuses down to a point deep within the pelvis, the prostate gland, the ovary, the broad ligament, and the paradidymis. These subsidiary paraganglia may attain a size of from 3 to 20 millimeters and present a histological structure very similar to that of the main adrenal organ, consisting of a capsule of connective tissue and a parenchyma made up of rounded masses of cells, supplied with nerves and a rich capillary network. They are often easily to be mistaken for lymph-nodes, an error soon corrected when the characteristic yellow or brownish color appears upon application of a solution of potassium bichromate. In the sympathetic plexuses and ganglia, chromaffin cells may occur singly or in groups. The latter, inclosed, *e.g.*, in the ganglia, either may or may not be separated from the nervous tissue itself by a sheath of connective tissue.

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[102] Wiesel: Wiener klinische Wochenschrift, 1906.
[103] Biedl: Innere Sekretion, vol. I, p. 358, 1913.

Gradual retrogression and diminution in size of many of the subsidiary paraganglia begins after birth. This applies in particular to the organ of Zuckerkandl, so that by the fifth to the eighth year of life its chromaffin property has been entirely lost. The chromaffin inclusions in the sympathetic ganglia, however, according to Wiesel, retrogress only very slowly and still exist in aged individuals. Special significance attaches to the subsidiary paraganglia in cases of malformation of the adrenals proper, where the former tissues may retain sufficient of their pristine importance and size to make up for deficient epinephrin production in the latter.

The *subsidiary interrenal tissues*, or *adrenal rests* often erroneously termed "accessory adrenals" formerly, the fact being overlooked that they contain no tissue corresponding to that of the medulla of the adrenals, arise either as persistent bits of that portion of the original interrenal tissue which ordinarily undergoes absorption when the cortex of the adrenal is formed, or by splitting off of small masses of the developing adrenal cortex through the intrusion of sympathetic cells or of bands of connective tissue. Their existence was known as far back as the seventeenth century. According to Schmorl[104] no less than 92 per cent. of all human cadavers, if carefully examined, will be found to show small or large aggregations of interrenal cells in various parts of the body. Histologically these consist, like the adrenal cortex, of a connective-tissue stroma in which are supported columns of cortical, lipoid-containing cells, usually arranged so as to form an outer glomerular, an intermediate fascicular, and occasionally also an inner reticular zone, as in the suprarenal organ itself. Like the adrenal cortex, moreover, these subsidiary interrenal bodies are capable, where the demand exists, *e.g.*, after excision of the adrenals, of undergoing a marked compensatory hypertrophy.

Three groups of subsidiary interrenal organs have been recognized by Poll.[105] The first group includes those found in the region of the adrenals and kidneys. Some occur in the substance of the adrenal cortex and medulla themselves. These may lie firmly imbedded at the surface of the adrenals and, when numerous, give the latter a nodulated appearance, or they may possess stalks connected with the interior parenchyma of the organ, or, again, they may lie more deeply, completely surrounded by parenchyma, even, *e.g.*, in the very center of the medullary tissue. They may be situated outside of the adrenals, in the adjacent connective tissue, or at the surface or in the interior of the kidney, in which location they sometimes become the source of the tumors known as hypernephromas. Along vessel walls they may be found in contact with the adrenal artery or vein, the inferior vena cava, or the renal vein, as well as between the vena cava and the aorta. They may also be noted in close relationship to the sympathetic nerve-plexuses, in the transverse mesocolic ligament (between the transverse colon and spleen), on the under surface of the liver or in its right lobe, and, lastly, in the pancreas. Poll's second group comprises subsidiary interrenal bodies found in the retroperitoneal space, below the inferior poles of the kidneys, along the internal spermatic veins, on the iliopsoas muscles in the vault of the pelvis, and on the sacroiliac synchondroses.

The third group consists of the interrenal tissues occurring in relation to the reproductive organs. Thus, in the male subject, such tissues may be found anywhere along the spermatic cord, above, below, or within the inguinal canal. They may occur between the testicles and epididymes. Wiesel[106] found such a collection of cells at the junction of the duct of the epididymis and the vas deferens in 76 per cent. of newborn babies; this tissue often persisted throughout life. Interrenal tissue has also been found imbedded in the testicular tissues and in the paradidymis. In the female subject, interrenal organs have been detected in the broad ligament, lying in contact with the Fallopian tube, and in the substance of the ovary. Biedl calls attention to the fact that subsidiary interrenal organs are encountered with relative frequency in the reproductive organs in the young and but seldom in old subjects, while Marchetti[107] makes the opposite assertion in the case of interrenal tissues in the vicinity of the adrenals themselves.

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[104] Schmorl: Ziegler's Beiträge, 9, 1891.

[105] Poll: Quoted by Biedl: Innere Sekretion, vol. 1, S. 356, 1912.

THE ADRENAL SECRETION IN RESPIRATION AND METABOLISM.

In the first Chapter it was shown that my interpretation of rôle of the adrenal secretion in respiration harmonized all the apparently divergent functions attributed by physiologists to these organs. The data in support of my interpretation will now be submitted:—

"It is, perhaps, wrong," writes Professor Duval, himself a prominent physiologist, "for physiologists to continue to only see in these phenomena mere results of endosmosis of liquids and of diffusion of gases through an inert membrane." As a clinician, I would urge that this theory is harmful in its far-reaching consequences. I have pointed out that the aërotonometer, upon which it is mainly founded, is a defective instrument, and that it is because of this that the results recorded by various physiologists have been divergent to such a degree that, in some instances, the diffusion of oxygen should occur, to correspond with its indication in the wrong direction, *i.e.*, from the hæmoglobin to the alveolar air, the tension of oxygen in the arterial blood being actually higher than the pressure of oxygen in the air-cells.

I characterize the prevailing theory as "harmful" because the physiologist, engrossed in his own field, does not realize that he is dealing with the foundation of probably the most important problem of our day in its influence over human life, viz., immunity not only in the tissues at large, but at the very threshold of infection—the pulmonary alveolar surface, and the alimentary canal, as will be shown later.

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[106] Wiesel: Sitzungsberichte der k. Akademie zu Wien, S. 108, 1899.
[107] Marchetti: Virchow's Archiv, No. 177, p. 227, 1904.

THE ADRENAL SECRETION IN PULMONARY RESPIRATION.—In the first edition of the present work (1903) I advanced the view, sustained by considerable evidence, that the adrenals took a leading part in the respiratory process by supplying a secretion which absorbed the oxygen of the air in the pulmonary alveoli, then became a part of the hæmoglobin and of the blood-plasma, which in turn carried it, as oxidizing principle, to all tissues.

Three years after this opinion was formulated, a noted English physiologist, Pembrey, wrote[14] in an impartial review of the recent advances in physiology and bio-chemistry: "It is impossible to give a satisfactory account of the gaseous exchange between the blood and the alveolar air." . . . "The body of evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen." This theory is that of Bohr, advanced in 1891, which attributes the oxygen-absorbing power and the excretion of carbon dioxide to active secretory processes carried on by the lining membrane of the air-cells. While the need of a secretion capable of absorbing the oxygen has been steadily growing in favor, however, the secreting membrane has not been found.

This is explained when the respiratory process is considered from my viewpoint: *It is not by a local membrane that the reducing secretion is produced, but by the adrenals.* As shown below, its properties and itinerary are precisely those required for the process, while its presence can be traced at every step to the hæmoglobin itself, of which it forms part.

A succinct review of the experimental evidence which has invalidated the diffusion doctrine, and of that upon which my conception of the respiratory process is based, will perhaps serve better than a prolonged analysis of the question (for which the reader is referred to previous editions) to convey the actual status of the question.

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[14] Pembrey: Hill's "Recent Advances in Physiology and Bio-Chemistry," p. 549, 1906.

Paul Bert,[15] thirty years ago, showed experimentally that the absorption of oxygen by the pulmonary blood persisted, even when the pressure of this gas was almost *nil.* Müller also observed that a strangulated animal exhausted the air in its lungs of *all* its oxygen, while Setschenow and Holmgren,[16] Zuntz,[17] and others found but traces of oxygen in the arterial blood of asphyxiated animals. This suggested that the diffusion doctrine was defective, and that the absorption of oxygen from the air was due to the presence, in the blood circulating through the lungs, of some substance capable of taking up this gas. This conclusion was sustained by the researches of Bohr,[18] Haldane and Lorrain Smith,[19] Vaughan Harley,[20] and Bohr and Henriques,[21] the last-named investigators referring to it as a substance "having greater avidity for oxygen than the blood itself" and presumably "a kind of internal secretion."

This view has been antagonized by some of the advocates of the diffusion theory (whose aërotonometric figures are suggestively discordant), but as we have seen the "evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen."

Having repeatedly noted the powerful reducing properties of adrenal extractives, it occurred to me that the secretion of the adrenals might fulfill this rôle. Anatomical studies in various lower animals and in man, and a systematic research in the literature of the subject, demonstrated that it met all the conditions required to satisfy so important a function.

The first deduction imposed by these researches was that

The secretion of the adrenals has a marked affinity for oxygen, and inevitably reaches the pulmonary air-cells.

Vulpian,[22] over fifty years ago, found that adrenal juice reduced iron perchloride and iodine. Cybulski[23] recorded a similar action on potassium permanganate; Langlois[24] noted, however, that adrenal extract lost its reducing properties *in vitro* when oxidizing compounds were added. As to the action of the atmospheric oxygen, Battelli[25] found that adrenalin did not lose its properties when contact with air was prevented, while Abel,[26] Takamine,[27] and others refer to this property as a source of trouble in laboratories, the latter chemist specifying, in fact, that adrenalin becomes oxidized by contact *with the air.*

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[15] Paul Bert: C. r. de l'Acad. des sci., Oct. 28, 1878.

[16] Setschenow and Holmgren, cited by Ludwig: Wiener med. Jahrb., 21st year, i, p. 145, 1865.

[17] Zuntz: Hermann's "Handbuch." iv, part 2, p. 43, 1882.

[18] Bohr: Skandin. Archiv für Physiologie, p. 236, 1891.

[19] Haldane and Lorrain Smith: Jour. of Physiol., xxii, No. 3, p. 231, 1897.

[20] Vaughan Harley: *Ibid.*, xxv, No. 1, p. 33, 1899.

[21] Bohr and Henriques: Arch. de physiol., ix, pp. 459 and 819, 1897.

[22] Vulpian: C. r. de l'Acad. des sci., p. 663, Sept. 29, 1856.

[23] Cybulski: Gazeta Lekarska, 2d series, xv, pp. 299-308, 1895.

[24] Langlois: Arch. de physiol. norm. et pathol., x, p. 124, 1898.

That the adrenal secretion inevitably reaches the air-cells was made clear by a study of the anatomical relations between the adrenals and the lungs. The blood of the efferent vessels of the adrenals, their veins, passes to the inferior vena cava, directly on the right side, and by way of the renal vein on the left. The actual presence of the adrenal secretion in the blood of the adrenal veins is shown by many experimental facts. Gottschau,[28] for example, traced hyaline granules (found subsequently to be their secretion) from the interior of the adrenals to their veins. This observation was confirmed and amplified by Manasse,[29] Aulde,[30] and Stilling.[31] Pfaundler[32] traced the same granules from the interior of the organ along the adrenal veins to the vena cava itself. It is doubtless the adrenal secretion and no other which is carried by the blood of the vena cava, for, when blood originating from the adrenals on its way to this great trunk was injected into animals by Cybulski and Scymonowicz,[33] it produced the characteristic effects of adrenal extract. These results were confirmed by Biedl,[34] Langlois,[35] and Dreyer.[36] Scymonowicz, Biedl, Dreyer, Salvioli, and Pizzolini[37] found, moreover, that such effects could not be obtained with venous blood obtained from other parts of the body.

The next fact to assert itself was that

On reaching the air-cells, the adrenal secretion absorbs oxygen and becomes a constituent of hæmoglobin and of the red corpuscles.

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[25] Battelli: C. r. de la Soc. de biol., liv, p. 1435, 1902.
[26] Abel: Bull. Johns Hopkins Hosp., p. 215, Sept.-Oct., 1898.
[27] Takamine: Therapeutic Gazette, p. 221, April 15, 1901.
[28] Gottschau: Arch. f. Anat. u. Physiol., Anat. Abth., p. 412, 1883.
[29] Manasse: Arch. f. Path. u. Physiol., cxxxv, p. 263, 1894.
[30] Aulde: Brit. Med. Jour., May 4, 1894.
[31] Stilling: Arch. f. path. Anat., clx, p. 324, 1897.
[32] Pfaundler: Sitzungsber. d. k. Akad. d. Wissensch. Mathem., cl, p. 3, 1892.
[33] Cybulski and Scymonowicz: Gazeta Lekarska, 2d series, xv, pp. 299-308, 1895; Archiv f. d. ges. Physiol., lxiv, Nos. 3 and 4, p. 97, 1896.
[34] Biedl: Archiv f. d. ges. Physiol., lxvii, part 9-10, 1897.
[35] Langlois: Arch. de physiol. norm. et pathol., ix, p. 152, 1897.
[36] Dreyer: American Journal of Physiology, ii, p. 203, 1899.
[37] Salvioli and Pizzolini: Gazetta degli osped., Mar. 23, 1902.

While a reducing substance has been found necessary, we have seen, to account for the absorption of oxygen from the alveolar air, it happened that the greater part of the hæmoglobin molecule was composed almost entirely of an albuminous substance which had remained unidentified. Gamgee,[38] for instance, states that "hæmoglobin exists in the blood-corpuscles in the form of a compound with a yet unknown constituent of the corpuscles." This body he defines as the "albuminous moiety of the hæmoglobin molecule" and,[39] as representing 96 per cent. of this molecule, the remaining 4 per cent. being the iron-laden hæmatin. Now, I found that this "unknown constituent" of hæmoglobin corresponded in its physicochemical properties with the adrenal secretion. Gamgee,[40] for example, states that hæmoglobin is insoluble in absolute alcohol, chloroform, benzol, ether, and all organic solvents: Vulpian[41] had already noted that, of all glandular products, that of the adrenals alone showed this peculiarity. Gautier,[42] Moore,[43] and Takamine also refer to it. Again, according to Moore and Purinton,[44] adrenal extracts are rapidly destroyed by alkalies; this is also a characteristic of hæmoglobin. This pigment likewise resists heat up to the boiling point; this applies also, according to Cybulski,[45] Moore,[46] and others to adrenal extract. Finally, Mulon[47] found that the red corpuscles gave the histochemical reactions of the active principle of the adrenals, thus showing that these blood-cells actually contain this principle. Since then the adrenal reaction has been obtained from blood-elements wherever sought, including that of the placenta.

In confirmation of this conclusion is the fact that

The oxygen-laden adrenal secretion is a constituent of the albuminous hæmoglobin in the blood-plasma.

Battelli[48] and Kraus[48a] found adrenalin in the blood, the latter author in Graves's disease. That this principle is a constituent of the albuminous portion of hæmoglobin voided by red corpuscles in the plasma suggested itself when Schmiedeberg,[49] Jaquet,[50] Abelous and Biarnès,[51] and other chemists showed that blood-plasma contains an oxidizing substance, subsequently known as oxidase. Not only was it found to resist heat at least up to the boiling point and to possess other chemical characteristics of the adrenal principle, but the actual presence of the latter is confirmed by other facts. Thus, in 1853, Traube had concluded that hæmoglobin could not fulfill the physicochemical functions ascribed to it without the aid of a catalyzer. Poehl[52] showed that the adrenal principle was a catalyzer, while Jolles[53] pointed out that the activity of a given volume of blood as a catalyzer corresponded with the number of red corpuscles it contained. It is because of this that Oliver and Schäfer found that oxidation of the adrenal principle does not occur in the blood; acting as a catalyzer it simply transfers oxygen from the pulmonary air to the tissues without being itself modified by the contact. Finally, Bernstein and Falta[54] have ascertained that "injections of adrenalin in healthy persons produced an increase of the consumption of oxygen and of the production of carbonic acid together with an increase of the respiratory quotient."

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[38] Gamgee: Schäfer's "Text-book of Physiology," I, p. 189, 1898.
[39] Gamgee: *Ibid.*, p. 207, 1898.
[40] Gamgee: *Ibid.*, p. 206, 1898.
[41] Vulpian: C.-r. de l'Acad. des Sci. de Paris, Sept. 29, 1856.
[42] Gautier: Chimie biologique, p. 355, 1892.
[43] Moore: Journal of Physiology, xvii, p. xiv, 1894-95.
[44] Moore and Purinton: American Journal of Physiology, iii, p. 15, 1900.
[45] Cybulski: Gazeta Lekarska, Mar. 23, 1895.
[46] Moore: *Loc. cit.*
[47] Mulon: Personal Communication.
[48] Battelli: C.-r. de la Soc. de Biol., liv, p. 1179, 1902.
[48a] Kraus: Cited by Brugsch, Folia Therapeutica, Jan., 1909.

Additional evidence to this effect and an explanation of the rôle of the red corpuscles were afforded by the next conclusion reached: That

The red corpuscles, after absorbing the oxygenized adrenal secretion (the albuminous constituent of their hæmoglobin) yield it to the blood-plasma in the form of droplets, the so-called "blood-platelets."

As Gamgee[55] teaches, hæmoglobin, under the influence of various chemical agents, "undergoes a decomposition of which the chief products are, an *albuminous* substance or substances, and a *coloring matter* which contains the whole of the iron"; but, as he also says, "the coloring matter of the red corpuscles is not extracted from them by the plasma." This does not, however, apply to their albuminous substance. That they discharge the latter in the plasma is rendered evident by various facts. Louis Elsberg,[56] thirty years ago, observed "a projection of a pediculated granule or knob" from the periphery of red corpuscles. Hirschfeld[57] traced these granules from the interior of these cells, through one or more minute apertures which closed up again, to the surrounding plasma. Brockbank[58] has published a beautiful microphotograph of "platelets in, or being extruded from, red cells." Again, Detemann[59] noted that the buds on the surface of the red cells "at first are attached to the cell by protoplasmic processes and contain hæmoglobin"; but that, "later, the buds become separated from the cell, losing their hæmoglobin." This does not militate against Gamgee's statement that the coloring matter remains in the corpuscles, but it indicates that the albuminous constituent is voided into the plasma.

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[49] Schmiedeberg: Archiv f. exper. Path. u. Pharm., vi, p. 233, 1876.
[50] Jaquet, cited by Salkowski: Archiv f. path. Anat., Jan. 4, 1897.
[51] Abelous and Biarnès: Arch. de physiol. norm. et pathol., 5th series, vii, pp. 195, 239, 1895.
[52] Poehl: Indian Lancet, May 23, 1904.
[53] Jolles: Münch. med. Woch., p. 2083, Nov. 22, 1904.
[54] Bernstein and Falta: Abst. in London Lancet, June 29, 1912.
[55] Gamgee: *Loc. cit.*, i, p. 189, 1898.

These albuminous droplets (which, in 1903,[60] I identified as the familiar *blood-platelets*), having absorbed oxygen in the lungs, should, in the light of preceding deductions and owing to the catalyzing property of their adrenal principle, be able to surrender their oxygen to any agent in the blood or tissues possessed of sufficient reducing power to appropriate it. That this applies to the droplets is shown by the reaction to certain stains. Litten[61] and others found, for example, that blood-platelets derived from the red corpuscles are best stained with methylene-blue; Stengel, White, and Pepper[62] state, in fact, that "methylene-blue gave the only positive results." This indicates that the droplets are certainly rich in oxygen—as their identity as the oxygenized adrenal secretion would suggest—for, as Ehrlich teaches, one of the conditions "essential to the methylene-blue reaction" is "oxygen saturation."[63]

A study of the melanins then showed that

The albuminous constituent of the hæmoglobin, or oxygen-laden adrenal secretion, is distributed by the red corpuscles to all parts of the body as an oxidizing agent.

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[56] Louis Elsberg: Annals of the N. Y. Acad. of Sci., i, 1879.
[57] Hirschfeld: Virchow's Archiv, clxvi, part 2, p. 196, 1901.
[58] Brockbank: Med. Chronicle, Mar., 1908.
[59] Determann: Deut. Archiv f. klin. Med., lxi, part 4, p. 365, 1898.
[60] Sajous: The present work, 1st ed., vol. i, p. 715, 1903.
[61] Litten: Deut. med. Woch., No. 44, Nov. 2, 1899.
[62] Stengel, White, and Pepper: Amer. Jour. Med. Sci., May 9, 1902.
[63] Quoted by L. F. Barker: New York Medical Journal, May 15 *et seq.*, 1897 to 1898.

Leonard Hill,[64] Hirschfeld, Chittenden and Albro,[65] and most classic writers look upon melanins, the brown and black pigments found in certain forms of sarcoma, in the tissues, the blood, the urine, etc., in various morbid states, as hæmoglobin derivatives. While Mörner, Brandl, and L. Pfeiffer[66] found that it contained iron, and accept this origin, Nencki and Berdez[67] do not, because they failed to find this metal in the pigment isolated from a melanotic sarcoma. These discordant opinions are harmonized, however, by the newer conception I submit: The first-named authors dealt with whole hæmoglobin, containing, therefore, its iron; while Nencki and Berdez dealt quite as surely with hæmoglobin, but only with its albuminous constituent.

Having traced to the adrenals the origin of the active agent of this albuminous hæmoglobin and this substance being melanin, the presence of the adrenal principle in melanins should be shown. In the first place these pigments were found by Walter Jones[68] insoluble in alcohol, ether, benzol, chloroform, etc., *i.e.*, precisely as Vulpian, Moore, and others had found to be the case with the adrenal principle. This applies as well to the action of alkalies, to which Jones, Abel and Davis[69] found melanins very sensitive, and to other tests. In the second place direct evidence was afforded by Boinet,[70] who found chemically that the bronze pigment of Addison's disease was identical to melanin, and also by Mühlmann,[71] who discovered independently that the Addisonian pigment was a product of the adrenals.

Finally, as the connection of the adrenal product with respiration and oxygenation I urge, suggests:—

An excess of adrenal secretion causes a rise of temperature.

This action was first observed by Oliver and Schäfer.[72] Reichert[73] recorded a rise of 1° C. in the dog, having reached this temperature "in less than forty minutes." In three experimental animals it "continued hypernormal for over two hours."

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[64] Leonard Hill: "Text-book of Chemistry," p. 374, 1903.
[65] Chittenden and Albro: Amer. Jour. of Physiol., ii, p. 291, 1899.
[66] Mörner, Brandl, and L. Pfeiffer, cited by Hammarsten: "Text-book of Physiological Chemistry," 5th American Ed., p. 688, 1908.
[67] Nencki and Berdez: *Ibid.*
[68] Walter Jones: Amer. Jour. of Physiol., ii, p. 380, 1899.
[69] Abel and Davis: Jour. of Exper. Med., i, p. 381, 1879.
[70] Boinet: Marseille méd., April 15, 1896.
[71] Mühlmann: Deut. med. Woch., No. 26, p. 409, 1896.
[72] Oliver and Schäfer: Jour. of Physiol., xviii, p. 230, 1895.
[73] Reichert: Univ. of Penna. Med. Bull., April, 1901.

Morel[74] noted a rise of 0.5° to 1° C. (0.9° to 1.8° F.) in guinea-pigs. Lépine[75] states that the increase of blood-pressure caused by adrenal extract is always followed by a rise of temperature. This is controlled by the familiar fact, first observed by Brown-Séquard, that removal of the adrenals is followed by a steady decline of temperature and by the hypothermia which attends Addison's disease.

Additional evidence on this particular feature of the general problem will be found in Volume II. I studied, for example, the evolution of the red corpuscles throughout the animal scale[76] and learned that they were tardy additions to the blood as storage cells when the hæmoglobin diffused in the plasma, as it is in many invertebrates and in certain low vertebrates, failed to satisfy the needs of the vital process. Having been brought to the conclusion that, contrary to what is now taught, it is the plasmatic hæmoglobin which carries oxygen to the tissues and not the red cells (though these act as storage cells for it as a constituent of their albuminous hæmoglobin), I traced this substance in various tissues and organs, including the nervous system, the guaiac and methylene-blue tests being those most frequently employed. Again, I found that the oxidases gave the reactions of the oxygen-laden adrenal secretion. Hence the term I applied to the latter: *adrenoxidase.*[77]

On the whole, this evidence, considered collectively, seems to me to afford a solid foundation for the conclusion that

It is the adrenal secretion which, after absorbing oxygen from the pulmonary air and being taken up by the red corpuscles, supplies the whole organism, including the blood, with its oxygen. It is, as such, the oxidizing constituent of the hæmoglobin, which, in turn, sustains tissue oxidation and metabolism.

It has been confirmed experimentally by Crile and Menten[78] and by Menten [78a] who found that adrenalin endowed venous blood with the power to become converted into arterial blood, and enabled hæmoglobin to become changed to oxyhæmoglobin.

Additional evidence in favor of this conception of the rôle of the adrenal secretion is afforded by the fact that it accounts, as will be shown by a few examples, for the properties of the adrenal secretion and preparations that the prevailing restricted view fails to explain.

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[74] Morel: Le Progrès médical, Aug. 3, 1903.

[75] Lépine: La Semaine médicale, Feb. 18, 1903.

[76] Sajous: The present work, p. 828

[77] Sajous: *Ibid.*, p. 822.

[78] Crile and Menten: Amer. Jour. of Physiol., vol. xxxviii, p. 225, 1915.

[78a] Crile and Menten: *Ibid.*, vol. xliv, p. 176, 1917.

Increased oxidation clearly accounts, for instance, for the observations of Reichert, Morel, Lépine and others, referred to above, that even non-toxic doses of adrenal extractives produce a *rise* of temperature, or those of Israel[79] which showed the great frequency of fever in tumors of the adrenals, or those of Courmont[80] in which adrenal grafts produced without the least evidence of infection what he characterized as a "formidable hyperthermia." In the latter cases it persisted until death occurred. Nor is it an ephemeral phenomenon, as is the case with the rise of blood-pressure, in the experimental use of adrenal preparations, for, as Reichert observed in his experiments, the high temperature persisted as much as two hours in some of the animals.

Again, adrenal preparations are said to raise the blood-pressure; but this occurs only under the influence of excessive doses or after their prolonged use. This effect becomes clear, however, when the adrenal secretion as the active constituent of hæmoglobin is regarded as the oxidizing agent of the tissues, and, as such, an active factor in metabolism. The muscular elements of the arteries being themselves the seat of increased metabolic activity, they are caused to contract, thus raising the blood-pressure. As shown by Oliver and Schäfer, however, there is also a direct action on the arterioles, and by Meltzer[81] a similar action on the endothelium of the capillaries. This local effect is due also to the enhanced metabolic activity of the adrenal product, its identity as catalyzer enabling it to activate oxidation in any tissue with which it comes into contact.

The excessive growth of children caused by hypernephroma also finds its normal explanation in the inordinate oxidation, due to the overproduction of adrenal secretion. F. de Mira[81a] found experimentally that the adrenals stimulated growth in general. The surplus of metabolic activity clearly accounts for the enhanced nutrition.

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[79] Israel, cited by Moffitt: Boston Med. and Surg. Jour., Oct. 8, 1908.
[80] Courmont: Congrès de Médecine Interne, Montpellier, 1898.
[81] Meltzer: Amer. Jour. Med. Sci., Jan., 1905.
[81a] F. de Mira: C.-r. de la Société de Biologie, Oct. 25, 1912.

In its relations to general diseases, the identity of the adrenals as the controlling agents of oxidation accounts for that ubiquitous symptom, *fever,* the mechanism of which has also remained obscure. This gives these organs a prominent place in pathology. Indeed, if the modern doctrine that fever up to a certain limit is the outward expression of an auto-protective or immunizing process is sound—and the bulk of evidence strongly sustains this view—the adrenals, as direct factors in fever, become also direct factors in protecting the body against disease. Their rôle in the economy thus assumes noble proportions in the extreme, since by their influence on tissue oxidation *the adrenals* sustain life, while through their participation in immunity they defend life.

Addison's disease may be due, as is well known, to tuberculosis, cancer, cirrhosis, and other organic disorders of the adrenals, or to pathologic changes in the solar plexus and semilunar ganglia. But *how* do these lesions cause the Addisonian syndrome in all its complexity? Many theories have been vouchsafed, but, in truth, as Anders[82] puts it, "the pathologic connection between the symptomatic phenomena of Addison's disease and the anatomic lesions has not been made out." Now, consider the disease with the adrenals as governing oxidation and metabolism: The adrenals being the seat of destructive lesions, these three conjoined functions increasingly show signs of deterioration; hence the low temperature and clamminess due to deficient oxidation; the marked and progressive asthenia, with great lassitude, due to inadequate metabolism in all muscles; the small and feeble pulse and weak heart action and steady lowering of the blood-pressure due also to inadequate metabolism in the cardiac and vascular muscles; the tendency to vertigo and the mental torpor due to ischæmia of the cerebrum, the result, in turn, of the general vasodilation and of the resulting withdrawal of blood into the deep vessels, and, finally, the bronzing, due likewise to vaso-relaxation and circulatory torpor, the latter entailing the deposition in the epidermis of what has been found chemically to be the oxidized adrenal product, *i.e.*, melanin.

The experimental production of glycosuria by injections of adrenalin reported by Blum, Croftan, Herter, and others is now familiar to every one. The labors of Pollak[33] have shown that, as I had previously suggested, this form of glycosuria was due to some relationship between the adrenal product and the hepatic glycogen. But what is this relationship? Here, again, the rôle of the adrenals in oxidation and metabolism supplies the explanation. By raising the blood's asset in oxygen, the adrenal active principle injected raises the rate of metabolic activity throughout the entire organism, including, of course, the pancreas. This organ being caused to secrete an excess of amylopsin, which in turn converts an excess of glycogen into sugar, the proportion of the latter in the blood soon exceeds the needs of the body, and the surplus is eliminated in the urine. The participation of the adrenals themselves in the process is controlled by various facts. Herter, for example, found that glycosuria was caused when the adrenals were compressed in such a way as to increase the outflow of secretion, while, conversely, ligation of the adrenal veins which transfer the secretion to the inferior vena cava caused the sugar to diminish rapidly.

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[82] Anders: "Practice of Medicine," p. 489, 9th ed., 1909.

On the whole, the facts submitted indicate that *the function now attributed to the adrenals,* i.e., *that of sustaining the tone of the vascular system, is but a feature of their true function: that of sustaining pulmonary and tissue respiration.*

Recent labors have added confirmatory evidence to that submitted. Thus, while Auer and Gates[33a] found that adrenalin was at once absorbed from the air-cells, raising the blood-pressure in five seconds, Bernstein and Falta[33b] noted that injections of adrenalin increased the intake of oxygen and the output of carbonic acid. Jackson[33c] observed a prompt dilatation of the bronchioles, and Januschke and Pollak[33d] an increase of the respiratory excursions, and in the depth of these, according to Nice, Rock, and Courtright[33e]. Finally, we have seen on page 67 that Crile and Menten and subsequently Menten proved experimentally the correctness of my earlier contention that adrenalin enabled hæmoglobin to become converted into oxyhæmoglobin in the lungs.

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[33] Pollak: Arch. f. exper. Path. u. Pharm., Bd. lxi, S. 149.
[33a] Auer and Gates: Jour. of Exper. Med., xxiii, 757, 1916.
[33b] Bernstein and Falta: London Lancet, June 29, 1912.
[33c] Jackson: Jour. of Pharm. and Exper. Ther., Mar., 1912.
[33d] Januschke and Pollak: Archiv. f. exper. Path. u. Pharm., lxvi, 205, 1911.
[33e] Nice, Rock, and Courtright: Amer. Jour. of Physiol., June 1, 1914.

THE GOVERNING CENTER OF THE ADRENALS.

That the functions of the adrenals are governed through nerves in the splanchnic is well known. Much evidence points to the posterior pituitary body as the origin of these nerves.

Removal of both hemispheres does not influence temperature, as shown by Frédéricq,[84] Goltz, and others. Corin and van Beneden[85] found in fact that, in decerebrated pigeons, the oxygen intake and the carbonic acid output did not differ from that of normal pigeons. Pembrey[86] states moreover that "the rapid rise in temperature which occurs when a hibernating marmot awakens is not prevented by removal of the cerebral hemispheres." This applies as well to so high a mammal as the dog, in which, as shown by Goltz,[87] removal of the hemispheres, including a part of the optic thalami and corpora striata (whose functions are also annulled by removal of the cortex, the impulses of which they transform and transmit), did not interfere with any purely vegetative function. Evidently, therefore, although the hemispheres and the basal ganglia can, when the seat of lesions, cause a rise of temperature, the heat center is not located in these organs.

The base of the brain, however, asserts itself as a pathway for thermogenic impulses. While Tschetschichin, in 1866, Schreiber,[88] and Reichert[89] located a thermoaugmentor center in the pontobulbar region, Ott,[90] Tangl,[91] and Sakowitsch[92] obtained a marked rise of temperature by producing lesions higher up, *i.e.*, in the floor of the third ventricle and the tuber cinereum. But, as Richet has long held, and as Schäfer[93] states, examination of such experiments shows that "the results are closely dependent upon the establishment of an irritative lesion in parts which are either directly in or in close proximity to the path taken by motor impulses." On the whole, the thermogenic lesions in the basal tissues must have irritated nerve-paths from some structure beneath the hemispheres.

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[84] Frédéricq: Arch. de biol., iii, p. 747, 1882.
[85] Corin and van Beneden: *Ibid.*, vii, p. 265, 1889.
[86] Pembrey: Schäfer's "Text-book of Physiology," i, p. 864, 1898.
[87] Goltz: Arch. f. d. ges. Physiol., li, p. 570, 1892.
[88] Schreiber: *Ibid.*, viii, p. 576.
[89] Reichert: Jour. Amer. Med. Assoc., January 18, 1902.
[90] Ott: Therap. Gaz., June 15, 1902.
[91] Tangl, cited by Ott: *Ibid.*
[92] Sakowitsch: Neurol. Centralbl., xvi, p. 530, 1897.
[93] Schäfer: *Loc. cit.*, ii, p. 717.

Further study of the question then showed that:—

The pituitary body sends nerve-fibers upward to the tuber cinereum and the walls of the third ventricle, and thence to the pontobulbar region and spinal cord.

As just shown, the heat center can only be located beneath the brain and basal ganglia. Now, anterior to the optic thalami, the corpora striata, and the seat of the thermogenic lesions produced by Ott and others, there exists no organ capable of generating nerve impulses by way of the tuber cinereum other than the pituitary body. The labors of many investigators in recent years have overthrown the view that any part of the pituitary body of man is vestigial. As Herring[94] concluded recently on histological grounds, "it is an organ of physiological importance." The various kinds of nerve-cells, neuroglia-cells, and ependyma-cells described by Berkley in the posterior lobe are of as great physiological importance, from my viewpoint, as any in the body at large. Cushing[95] recently confirmed by a large number of experiments the fact previously emphasized by many investigators, that complete removal of the pituitary invariably produced death.

Sappey, Luschka, Müller, and others of the older anatomists refer to the presence of nerve-fibers passing from the pituitary body along its pedicle, up to the third ventricle. But it was only after the Golgi method had been introduced that this fact could be placed on a solid basis. Ramon y Cajal[96] then found that the fibers passed upward to a large nucleus behind the optic thalami. Joris[97] also found histologically that "numerous fibers descend in parallel lines along the pedicle of the pituitary. They do not all come from the retro-optic nucleus," he writes; "some come from regions *posterior* to the infundibulum". . . Bearing directly upon the production of thermogenic impulses is the discovery by Gentès[98] of fibers which pass from the pituitary to the tuber cinereum. Andriezen[99] had also traced, in the white mouse, fibers from the pituitary to the pons.

We thus have a direct nerve path from the pituitary to the pontobulbar region—the identical tract along which, at various points, the lesions produced by Ott, Tangl, Sakowitsch, and Reichert provoked a marked rise of temperature. We will see presently that this path is continued down the cord, and that it eventually reaches the adrenals.

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[94] Herring: Quarterly Jour. of Exp. Physiol., i, No. 2, 1908.
[95] Cushing: Jour. Amer. Med. Assoc., p. 249, 1909.
[96] Ramon y Cajal: Anales de la Soc. española de hist. nat., 2a Seria, xxiii, p. 214, 1894.
[97] Joris: Mém. Couron. de l'Acad. Roy de Belgique, xix, part 10, 1906.
[98] Gentès: C. r. de la Soc. de biol., lv, p. 1560, 1903.
[99] Andriezen: British Medical Journal, January 13, 1894.

The next feature determined was a striking functional correlation between the pituitary and the adrenals. Schäfer and Herring[100] have emphasized this parallelism not only as to their function, but also as to their development and structure. I ascertained, for example, that

The pituitary, like the adrenals, influenced general oxidation and the temperature, and also general metabolism and nutrition.

Although removal of the hemispheres does not influence the temperature, as we have seen, removal of the pituitary deeply affects this process. Marinesco[101] and Vassale and Sacchi[102] observed that it was followed by increasing hypothermia. This cannot be ascribed to operative shock, for Masay[103] first trephined the sella turcica to expose the pituitary, and allowed the animal to recover after this—the most violent step of the experiment. The result of subsequent removal was the same. Andriezen[104] and other authors also refer to a steady decline of temperature. Paulesco[105] noted that this decline was progressive until death occurred. Pirrone[106] states that the main symptoms are referable to the "vascular and respiratory systems and the temperature." The relationship with the respiratory process is further shown by the marked disturbances of this class, dyspnœa, polypnœa, etc., noted by Cyon, Andriezen, Masay, and other experimenters.

The impairment of general metabolism through deficient oxygenation must necessarily inhibit nutrition. Practically all investigators refer to rapid emaciation and cachexia as prominent symptoms. In a dog which survived sixteen days' removal of the organ, Thaon[107] observed "a progressive emaciation, followed by death in extreme cachexia." Caselli,[108] Pirrone,[109] and Masay[110] also allude to this phenomenon. Fuchs[111] and many other authors urge the close—though obscure—relationship between the pituitary and bodily metabolism. Striking evidence of the influence of the pituitary on metabolism and nutrition is afforded by its rôle in gigantism and acromegaly, the excessive growth during the period of hyperplasia of the organ, and the steady decline from the time degeneration of its anterior lobe begins. A relationship with the adrenals is suggested, moreover, by a familiar symptom of the cachectic stage of acromegaly, of which Harlow Brooks[112] says: "A general brownish pigmentation is present in the average case, which at times strongly resembles that found in Addison's disease."

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[100] Schäfer and Herring: Philos. Transactions, cxcix, p. 29, 1906.
[101] Marinesco: Bull de la Soc. de biol., p. 509, June 4, 1892.
[102] Vassale and Sacchi: Arch. ital. de biol., xxii, p. 123, 1895.
[103] Masay: Arch. de la Soc. roy. de sci. méd. et nat. de Bruxelles, xii, part 3, p. 1, 1903.
[104] Andriezen: *Loc. cit.*
[105] Paulesco: Jour. de physiol. et de path. gén., No. 3, p. 441, 1907.
[106] Pirrone: Riforma medica, February 25, 1903.
[107] Thaon: L'Hypophyse, p. 90, 1907.

Another feature attesting to the parallelism between the pituitary and the adrenals is that

The pituitary, like the adrenals, influences the blood-pressure.

Cyon[113] and subsequently Masay[114] found that excitation of the exposed pituitary caused a marked rise of blood-pressure—from 81 to 200 mm. Hg. in one instance. Masay attributed this action to the presence in the organ of a secretion which the excitation and accompanying pressure forced into the circulation. While no one can assert today that such a secretion is not produced by the pituitary body, the actual existence of such a secretion or its functions has not so far been demonstrated. The substance considered as such is rich in albuminous hæmoglobin, and it is the adrenal principle it contains which, in my opinion, causes the rise of blood-pressure obtained by injections of the extract. When the pressure is marked, the kidneys, being passively congested, dilate, and diuresis is caused. The effects observed experimentally are thus accounted for without the need of a secretion to do so. This applies also, from my viewpoint, to several so-called "internal secretions." Testicular juice or orchitic extract, for instance, is an oxidizing ferment and catalyzer; it is found in all tissues, in the female as well as in the male; it gives crystals of hæmin with Florence's test, etc., and other reactions peculiar to the adrenal and thyroid principles—both of which are also found in all tissues. A close examination of Masay's report, moreover, does not sustain his opinion that the rise of blood-pressure is to be ascribed to a secretion produced by the pituitary. The rise of pressure was *instantaneous* and general—a fact which points either to vasoconstriction through nerves or to the action of some intensely active and evanescent principle. Both these factors are available. Not only is the pituitary known to be related with the sympathetic system, but Langley[115] has called attention to the remarkable fact that "the effects produced by adrenalin upon any tissue are such as follow excitation of the sympathetic nerve which supplies the tissue," a conclusion confirmed by several observers. This paradoxical fact is clearly explained by the presence of the adrenal principle in the hæmoglobin. When Cyon and Masay excited the pituitary, therefore, they merely caused sympathetic constriction of all arterioles, including their offshoots the vasa vasorum; the walls of all vessels receiving an excess of albuminous hæmoglobin (adrenoxidase) they contracted, thus causing a rise of blood-pressure.

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[108] Caselli: Studi anat. e sperim. sulla fisio-pat. della glandula pituitaria, 1900.

[109] Pirrone: *Loc. cit.*

[110] Masay: *Loc. cit.*

[111] Fuchs: Wiener med. Woch., February 8, 1903.

[112] Harlow Brooks: Archives of Neurol. and Psychol., i, p. 435, 1898.

[113] Cyon: Arch. de physiol., x, p. 618, 1898.

[114] Masay: *Loc. cit.*

Again, as is well known, the adrenals are intimately connected with the abdominal ganglia and are, embryologically, sympathetic structures. Their vessels being likewise influenced, a sudden excess of secretion furnished a second cause for the ephemeral rise of blood-pressure observed by Masay. The power of the adrenal secretion to cause such a rise is generally recognized. Schäfer[116] characterizes as "astounding" the minuteness of the dose of adrenal extract that will excite physiological effects; 5.7 millionths of a gramme of Abel's epinephrin sulphate to each kilo of body weight was found by Reid Hunt[117] to cause a rise of blood-pressure of 66 mm. Hg. As to the action on the heart, Oliver and Schäfer[118] found, as is well known, that adrenal products not only acted directly on the muscular walls of blood-vessels, causing them to contract (which accounts for the rise of blood-pressure), but also upon the muscular wall of the heart. Finally, the rise of pressure is undoubtedly produced by the adrenalin extract itself, for Strehl and Weiss[119] found that clamping of the adrenal veins lowered the blood-pressure, while release of these vessels restored it to its previous level.

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[115] Langley: Hill's Recent Advances in Physiology, p. 584; 1906.
[116] Schäfer: Textbook of Physiology, i, p. 957, 1898.
[117] Reid Hunt: Amer. Jour. of Physiol., v, p. 7, 1901.
[118] Oliver and Schäfer: Jour. of Physiol., xvi, p. 1, 1894; xvii, p. 9, 1895

Another suggestive fact attesting to the pituitaro-adrenal parallelism is that

The pituitary, in keeping with the adrenals, gives rise to glycosuria.

Adrenal extractives, as observed by Blum,[120] Croftan,[121] Metzger,[122] Herter, and others, cause glycosuria. The adrenal secretion evidently provokes the phenomenon also, for Herter and Wakeman[123] found that compression of the adrenals, by increasing the outflow of secretion into the adrenal veins, caused glycosuria, while, conversely, adrenalectomy was followed by a marked diminution of the sugar in the blood. Again, we have seen that the adrenal secretion passes from the adrenal veins into the inferior vena cava; Kauffmann[124] found that when this great vessel was ligated the sugar diminished rapidly, both in the blood and in the urine.

Now, the influence of the pituitary over glycosuria is quite as marked. M. Loeb[125] urged, over twenty years ago, that the glycosuria which accompanies so often tumors of the pituitary should not be ascribed to mere coincidence. Marie observed it in over one-half of his cases of acromegaly. Borchardt[126] tabulated 176 patients with this disease, 71 of whom had glycosuria; as I had five years earlier,[127] he ascribes this symptom to overactivity of the pituitary, and its cessation to final degeneration of this organ. In 16 reported cases studied by Launois and Roy[128] each subject presented at the autopsy a tumor of the pituitary. That the glycosuria is not due to pressure of the enlarged organ upon the basal or bulbar tissues is shown by the fact that it can be produced in a normal organ. Thus, F. W. Pavy[129] found that,

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[119] Strehl and Weiss: Pflüger's Archiv, lxxxvi, p. 107, 1901.
[120] Blum: Deut. Archiv f. Med., lxxi, Nos. 2 u. 3, p. 146, 1901.
[121] Croftan: American Medicine, January 18, 1902.
[122] Metzger: Münch. med. Woch., xlix, p. 478, 1902.
[123] Herter and Wakeman: Amer. Jour. Med. Sci., January, 1903.
[124] Kauffmann: Arch. de physiol., viii, p. 150, 1896.
[125] Loeb: Centralbl. f. inn. Med., September 3, 1886.
[126] Borchardt: Zeit. f. klin. Med., lxvi, No. 4, 1908.
[127] Sajous: *Loc. cit.*, i, p. 386, 1st edition, 1903.
[128] Launois and Roy: C. r. de la Soc. de biol., lv, p. 382, 1903.
[129] Pavy: Proc. Royal Soc. of London, x, p. 27, 1859.

"of all the operations on the sympathetic of the dog that have yet been performed, removal of the superior cervical ganglion the most rapidly and strongly produces diabetes." This enigmatic result finds its explanation in the light of the conclusions I have submitted: The superior cervical ganglion, as is well known, supplies vasoconstrictor filaments to the pituitary; removal of this ganglion by causing relaxation of its arteries causes the organ to become hyperæmic and therefore overactive, with glycosuria as a result. Control of this conclusion is afforded by the fact that, as in all exacerbations of activity thus induced, the symptom was fleeting, as shown by Pavy's statement that the glycosuria was "only of a temporary nature."

Having now ascertained 1, that the pituitary could alone be the source of impulses to the adrenals; 2, that this organ projected fibers toward the bulb, and, 3, that the pituitary and the adrenals gave rise to similar experimental and clinical phenomena, it became a question whether a nerve-path actually united these organs. Study of this question showed that

The phenomena provoked by both the pituitary and the adrenals can be traced by irritation or sections along a continuous path leading from the pituitary to the adrenals.

The tuber cinereum, which, we have seen, receives fibers from the pituitary, extends backward toward the bulb. Punctures along the upper part of this path by Ott, Tangl, and others not only raised the temperature and quickened the respiration, but a section below the same region by Sawadowsky[130] and Ott and Scott[131] rendered impossible the production of fever by agents known to produce it. Caselli,[132] moreover, found that irritation of the same tissues produced glycosuria.

The nerve-path continuing downward, we meet in the pontobulbar region the thermogenic center of Tscheschichin, Schreiber, and Reichert. Suggestive in this connection is the fact that Bruck and Günther[133] found that simple puncture with a probe between the pons and medulla not only caused a marked rise of temperature, but that this rise was general. The respiratory center is a familiar classic feature of the medulla; we have seen how all the phenomena evoked by the adrenals are linked with the respiratory process. All this applies as well to Claude Bernard's puncture in the same region as a cause of glycosuria, and due in the light of all this evidence to irritation of the path from the pituitary to the adrenals.

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[130] Sawadowski: Centralbl. f. d. med. Wissen., xxvi, pp. 145, 161, 1888.
[131] Ott and Scott: Jour. of Exper. Med., November, 1907.
[132] Caselli: *Loc. cit.*
[133] Bruck and Günther: Arch. f. d. ges. Physiol., iii, p. 578, 1870.

In the upper portion of the spinal cord, division by Tscheschichin,[134] Bernard,[135] and Pochoy,[136] respectively, in various animals sent the temperature down 7° to 16° C. in from four to twenty-four hours, death following in Pochoy's animals. Riegel[137] found that production of heat was diminished. That glycosuria is produced through efferent fibers passing downward in the upper cord is shown by the well-known fact, mentioned by Stewart,[138] that puncture of the bulb does not cause glycosuria if "the spinal cord above the third or fourth dorsal vertebra be cut before the puncture is made."

This level of the cord is of special interest, since it is here that the nerve-path to the adrenals leaves the spinal cord. Here can be evoked a rise of blood-pressure occurring in excess of that due to vasomotor nerves. Thus, François-Franck and Hallion[139] obtained a rise of pressure by exciting the five upper dorsal rami, and also by stimulating the corresponding segment of the sympathetic chain, although the vasoconstrictor nerves to the organ studied, the liver, was known to reach this organ through a lower ramus, the sixth—a limit confirmed by Langley.[140] But they could not account for this phenomenon. Bulgak, Bunch,[141] Jacobi,[142] and others also obtained marked vasoconstrictor effects by exciting these upper rami, although the vasomotor nerves to the organs influenced were known to leave the cord lower down. In other words, a duplicate source of vasoconstriction, as it were, was present whose nature remained obscure. It was brought to light, however, by the fact that Jacobi[143] found that excessive *inhibitory constriction of the intestinal vessels ceased*, and was replaced by normal vasoconstriction when he severed the nerves to the adrenals. The intense action of their secretion on the blood-pressure clearly accounts, from my viewpoint, for the excessive constriction observed.

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[134] Tscheschichin: Arch. f. Anat., Physiol., u. wissensch. Med., p. 151, 1866.
[135] Bernard: Leçons sur la chaleur animale, p. 161, 1876.
[136] Pochoy: Thèse de Paris, 1870.
[137] Riegel: Archiv f. d. ges. Physiol., v, p. 629, 1872.
[138] Stewart: Manual of Physiology, p. 452, 1900.
[139] François-Franck and Hallion: Arch. de physiol., viii, No. 5, p. 934, 1896.
[140] Langley: Schäfer's Textbook of Physiology, ii, p. 344, 1900.
[141] Bunch: Jour. of Physiol., xxiv, p. 72, 1899.
[142] Jacobi: Arch. f. exper. Path. u. Pharmakol., xxix, p. 171, 1892.
[143] Jacobi: *Ibid.*

Briefly, these facts indicate jointly that

The pituitaro-adrenal path leaves the spinal cord through the upper four or five rami, to enter the sympathetic chain, and then the great splanchnic, which, through the intermediary of the semilunar ganglia, supplies nerves to the adrenals.

That this path is the true one is shown by additional data. Thus, Goltz and Ewald[144] found that animals deprived of their spinal cord from the bulb down could live a long time—years even—but that they showed a striking peculiarity, even after their vessels had resumed their normal caliber, that of dying of cold. Ott[145] found, however, that the animals were able to generate their usual heat when the section was made *below* the fifth dorsal vertebra. This is evidently because the pituitaro-adrenal nerve-paths had left the cord above this level to pass over to the sympathetic chain and the splanchnic, for, although Biedl[146] had failed to increase the secretory activity of the adrenals by exciting electrically all the median and lower dorsal rami, both he and Dreyer[147] had succeeded in doing so by stimulating the great splanchnic nerve. Proof of this is afforded by the fact that the greater splanchnic also transmits impulses to the adrenals which provoke glycosuria, for Laffont[148] caused it by stimulating this nerve. Moreover, it is evidently through a nerve-path starting at least in the medulla that glycosuria is caused; for Eckhard, Kauffmann,[149] and others found that even the glycosuria caused by Bernard's puncture ceased when the greater splanchnic was severed. There can be no doubt that it is through the adrenals that the glycosuria is caused, for, besides the evidence I have already adduced to this effect, A. Mayer[150] found that Bernard's puncture failed to produce this symptom after removal of the adrenals.

On the whole, all the evidence, of which the foregoing is a part, seems to me to have shown:—

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[144] Goltz and Ewald: Archiv f. d. ges. Physiol., lxiii, pp. 362, 400, 1896.
[145] Ott: Textbook of Physiology, p. 348, 1904.
[146] Biedl: Arch. f. d. ges. Physiol., lxvii, No. 9-10, p. 443, 1897.
[147] Dreyer: Amer. Jour. of Physiol., ii, p. 203, 1899.
[148] Laffont, cited by Laulanié: Éléments de physiologie, 2d ed., p. 943, 1905.
[149] Kauffmann: C. r. de la Soc. de biol., p. 284, 1894.
[150] Mayer: Arch. gén. de méd., July 17, 1906.

1, That the pituitary is connected with the adrenals by direct nerve paths; 2, that it thus governs, through the adrenals, general oxidation, metabolism, and nutrition.

The secretory function of the pituitary will be reviewed later.

HYPOADRENIA.

This designation is submitted as a more exact one than the term "hypoadrenalism" now increasingly used. The latter suggesting to the uninitiated that the condition it describes is one of habitual insufficiency of the adrenals is misleading, since the secretory activity of these organs is subject at all times, even where advanced lesions exist, to fluctuations. The phrases "insufficiency of the adrenal" and "adrenal insufficiency" portray more acceptably the true condition present, but they are as ill calculated to designate this condition from a scientific standpoint as would "deficiency of red corpuscles" for anemia.

While we owe to Addison, a clinician, the first observations (1855) which indicated that the adrenals were of signal importance to the welfare of the organism it was Brown-Séquard, a physiologist, who (1856), we have seen, first demonstrated their true importance to life. The symptoms caused by a deficient production of adrenal secretion were not, however, erected to the rank of a special syndrome quite independent of, and capable of occurring without the presence of, Addison's disease, and as a manifestation of other diseases, until Sergent and Bernard[151] did so in 1899.

Viewed from my standpoint, however, the symptom-complex of this condition is subject to quite a different interpretation than the prevailing one, all the labors anterior to my own having taken as foundation only two functions: that of sustaining the cardio-vascular tone (Oliver and Schäfer), and that of producing an antitoxic substance capable of neutralizing toxic products of muscular activity, and other undetermined poisons (Abelous and Langlois). The processes through which these effects are brought about having remained obscure, however, more or less empirical conceptions have had to be employed to fill the gaps. Thus, the muscular asthenia in Addison's disease is attributed to the toxic effects of the muscular poisons that the adrenals in their normal state should have destroyed, while, to explain bronzing, irritation of the sympathetic plexuses around the adrenals has to be invoked. The hypothermia, dyspnœa, and other symptoms are indifferently attributed to the low blood-pressure or to the intoxication. If we ask, however, *how* irritation of the sympathetic plexus produces bronzing, or *why* after adrenalectomy the temperature, both rectal and peripheral, steadily declines, or fathom to any depth the explanations that are furnished, it soon becomes apparent that some important factor is missing.

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[151] Sergent and Bernard: Archives gén. de méd., July, 1899.

It is this factor which my labors seem to me to have supplied. They afford an explanation of all the symptoms brought on by inadequate functional activity of the adrenals. Being based primarily upon the array of experimental data submitted in the earlier portion of this chapter, they also constitute a foundation for a more exact conception of the various disorders of the adrenals than the prevailing teachings afford.

Another feature which my interpretation of the functions of the adrenals seems to me to elucidate, as will be shown in a special chapter, is the process through which these organs carry on antitoxic functions other than those concerned with toxic wastes of muscular origin. This property, observed by Albanese,[152] who noted a decreased resistance of decapsulated frogs to neurine as compared to normal frogs, was first placed on a solid footing by the researches of Abelous[153] and Langlois, which showed similar results with atropine in the frog, and strychnine and curare in the rabbit, though less marked. Charrin and Langlois[154] then found that the addition of adrenal extract to nicotine *in vitro* reduced the toxic activity of the latter, and that injected nicotine was also less poisonous when adrenal extract was added to it. Oppenheim[155] then obtained uncertain results with potassium arsenate and atropine, but marked results with phosphorus, guinea-pigs in which the injection of this toxic was followed by that of adrenal extract surviving from two to four times longer in some instances, and altogether in others. Strychnine, $^1/_{60}$ grain, which killed guinea-pigs in three and four minutes, produced but few spasms and proved harmless as to life when its injection was followed a minute later by one of 2 c.c. of adrenal extract. A larger dose of strychnine ($^1/_{48}$ grain) proved fatal, however. These and other experiments with various toxins led Oppenheim to conclude that "the adrenals, which normally destroy poisons elaborated during muscular work, assume great importance during pathological states and must be classed among the most useful of protective organs."

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[152] Albanese: Arch. Italiennes de Biol., pp. 49 and 338, 1892.

[153] Abelous: Rev. Générale des Sciences, May 15, p. 273, 1893, and Bull. de la Soc. de Biol., April 2, 1898.

[154] Charrin and Langlois: Bull. de la Soc. de Biol., p. 708, 1896.

[155] Oppenheim: Bull. de la Soc. de Biol., March 23, 1901; also "Les Capsules Surrénales. Leur fonction antitoxique," Paris, 1902.

On the whole, in the light of the personal views submitted, hypoadrenia or insufficiency of the adrenals means far more than the effects of lowered blood-pressure and the adequate destruction of muscular wastes; *it means besides: inadequate oxidation and therefore imperfect tissue metabolism and nutrition, and also impairment of the auto-protective functions of the body at large.*

The bearing of this conclusion will be gradually developed while analyzing the three clinical forms into which I have divided hypoadrenia,—a classification which appears to me necessary to enable us to apply prophylactic and remedial measures judiciously. These three forms are the following:—

1. *Functional hypoadrenia,* a form in which the adrenals, though not the seat of organic lesions, are functionally deficient because of tardy development, debilitating influences such as fatigue, starvation, etc., and old age;

2. *Progressive hypoadrenia, or Addison's disease,* a form in which the functions of the adrenals or of their secretory nerves are progressively impaired by organic lesions, tuberculosis, cancer, fibrosis, etc.;

3. *Terminal hypoadrenia,* a form which occurs as a more or less tardy complication of infectious diseases and toxæmias, owing to exhaustion of the secretory activity of the adrenals during the earlier and febrile stage of the causative disease.

FUNCTIONAL HYPOADRENIA.

The adrenals playing so important a rôle in the maintenance of the life process itself, it is obvious that, apart from any organic lesion in these organs, any marked depression of their functional activity should manifest itself by symptoms corresponding with this depression. To the symptom-complex of this condition I have given the name of "functional hypoadrenia" to distinguish it from the forms due to destructive disorders of the adrenals, which constitute Addison's disease, and offer, of course, a far graver prognosis. As a definition of this condition, I would submit that

Functional hypoadrenia is the symptom-complex of deficient activity of the adrenals due to inadequate development, exhaustion by fatigue, senile degeneration, or any other factor which, without provoking organic lesions in the organs or their nerve-paths, is capable of reducing their secretory activity. Asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anæmia, slow metabolism, constipation, and psychasthenia are the main symptoms of this condition.

The field covered by functional hypoadrenia is necessarily a vast one, since it includes the asthenias so often met with in the four main stages of life: infancy, childhood, adult, and old age, usually attributed to "weakness" or "exhaustion," and often "neurasthenia," which have been traced to no tangible cause. All I can submit herein, therefore, is a cursory analysis of the subject.

FUNCTIONAL HYPOADRENIA OF INFANCY AND CHILDHOOD.—Although the adrenals are relatively large in the infant (one-third the size of the kidney at birth), their functions are limited to the carrying on of the vital process, at least during the first year of life, the mother's milk supplying the antitoxic products capable of protecting it against the destructive action of poisons of endogenous and exogenous origin. This protective influence of maternal milk is clearly defined in the following quotation from Prof. William Welch's Harvey Lecture: "It is an important function of the mother to transfer to the suckling, through her milk, immunizing bodies, and the infant's stomach has the capacity, which is afterward lost, of absorbing these substances in active state. The relative richness of the suckling's blood in protective antibodies as contrasted with the artificially fed infant explains the greater freedom of the former from infectious diseases." Striking proof of this is afforded by the fact that during the siege of Paris in 1870-71, according to J. E. Winters,[156] "while the general mortality was doubled, that of infants was lowered 40 per cent. owing to mothers being driven to suckle their infants."

The predilection of children to certain infectious diseases obviously indicates that it is not only in infancy that vulnerability to these disorders exists; it exposes life during the first decade, and more, of the child's existence. If, then, in the infant the maternal milk, as Welch says, protects the suckling against such diseases, at least to a considerable extent, we must conclude that the same underlying cause of vulnerability persists several years, *i.e.*, until it has in some way been overcome. How this occurs we have seen. The adrenals acquire, with other organs, we shall see, the power to supplant the mother in contributing antitoxic bodies to the blood; they supply internal secretions which fulfill this rôle.

These facts point to the adrenals as at least prominent organs among those whose inadequate development explain the special vulnerability of children to certain infections, the "children's diseases." It becomes a question now whether there are degrees of this hypoadrenia which render the child more or less liable to infection.

That degrees of hypoadrenia exist in children is in reality a familiar fact to every physician when the signs of this condition are placed before him. The ruddy, warm, hard-muscled, heavy, out-of-door, romping child with keen appetite and normal functions, is one in whom the adrenals are as active as the development commensurate with its age will permit. He is ruddy and warm because oxidation and metabolism are perfect and the blood-pressure sufficiently high to keep the peripheral tissues well filled with blood; his muscles, skeletal, cardiac, and vascular, are strong because, in addition to being well nourished, they are exercised and well supplied with the adrenal secretion, which, as shown by Oliver and Schäfer, sustains muscular tone. As normal outcome of this state, we have constant stimulation of the functional activity of the adrenals. The muscular exercise and maximum food intake involve a demand for increased metabolism and oxidation, and the resulting greater output of wastes imposes upon the adrenals, as participants in the oxidation and auto-protective processes, greater work, more active growth and development, *with increase of defensive efficiency* as normal result.

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[156] Winters: "Practical Infant Feeding," p. 6.

The pale, emaciated, or pasty child with cold hands and feet, flabby muscles, whose appetite is capricious or deficient—the pampered house-plant so often met among the rich—represents the converse of the healthful child described, just as does the ill-fed, perhaps overworked child of the slums. The emaciation, the cold extremities, indicate deficient oxidation, metabolism and nutrition owing to the torpor of the adrenal functions; the pallor is mainly due to a deficiency of the adrenal principle in the blood and to the resulting low blood-pressure, which entails retrocession of the blood from the surface. This child is not ill, but the hypoadrenia which prevails normally, owing to the undeveloped state of its adrenals, is abnormally low, and it is vulnerable to infection.

That all conditions which in the adult tend to produce functional hypoadrenia affect the child at least to the same extent is self-evident.

FUNCTIONAL HYPOADRENIA IN THE ADULT.—As in the child, the adrenals may be inherently weak. Such subjects do not, as in hypothyroidia, show signs of myxœdema; but their circulation and heart action are feeble, they tend to adiposis, and show other signs of hypoadrenia. I have witnessed suggestive bronze spots in such cases. As a rule, however, the development of the adrenals in adults is an accomplished fact—as also that of their coworkers in the immunizing process, the thyroid and pituitary, we shall see. The adrenals, fully capable of sustaining oxidation and metabolism, are able to defend the organism adequately; indeed, they do more: by sustaining oxidation and metabolism up to its highest standard in all organs, they also preserve the efficiency of all other defensive resources, including phagocytosis, with which the body is endowed to their highest level. On the whole, the *normal adult whose adrenals functionate normally is relatively resistant to infection.* The infrequency with which the physician is infected, notwithstanding daily exposure in his professional work, attests to this fact.

Functional hypoadrenia appears, however, when, irrespective of any disease, and as a result of the vicissitudes of our existence, the adrenals are exhausted by the excessive secretory activity that exaggerated labor or exercise imposes upon them.

Fatigue is a prominent factor in this connection. Mosso's ergograph shows clearly the functional efficiency of the forearm. If by means of this instrument we compare the muscular power of a case of Addison's disease with that of any other kind of sufferer whose muscles are organically normal, a striking difference will be noticed: signs of fatigue appear very soon, and muscular impotence asserts itself where an advanced case of tuberculosis, for example, will be able to show appreciable strength. Intense asthenia is, in fact, a symptom of Addison's disease almost as characteristic as the bronze spots. It is as pre-eminent after experimental removal of both adrenals. This harmonizes with Oliver and Schäfer's demonstration of the influence of the adrenal secretion over muscular tone. Many other proofs could be adduced to show that there is a close relationship between fatigue and the functions of the adrenals. The pale and drawn face of an exhausted man, the readiness with which he suffers from the effects of cold and exposure, especially in the intestines, are familiar features of daily life.

The unusual prevalence of disease among soldiers in the field is of course partly due to the defective sanitation that a campaign entails; but fatigue—particularly that due to heavy marching, carrying heavy accoutrements—is, in my opinion, an important predisposing cause, through its influence upon the adrenals. Not only are these organs called upon to sustain general oxidation and metabolism at a rate exceeding by far that which amply suffices for normal avocations, but the fact that, as shown by Abelous and Langlois,[157] they also serve to destroy the toxic products of muscular activity constitutes another cause of drain upon their secretory resources. "Fatigue," write Morat and Doyon,[158] referring to experimental fatigue in animals deprived of their adrenals, "has an aggravating influence, as first indicated by Abelous and Langlois, and confirmed by Albanese and all authors. Hultgren and Andersson have even observed sudden death as a result of powerful movements of the body." Sézary[158a] has termed "hypoepinephry" a permanent inability of the adrenals to protect the body against infection.

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[157] Abelous and Langlois: *Loc. cit.*

[158] Morat and Doyon: "Traité de Physiologie," Art. "Sécrétions Internes," p. 441, 1904.

Debility from any source: starvation, loss of blood, etc., as efficiently renders the body vulnerable to disease: "Combine toxin and antitoxin, and inject the mixture," writes Prof. Charrin;[159] "no harm will follow. But weaken the animal by starvation or slight bleeding and administer the same injection; death will follow with all the signs of poisoning by the toxin, with congested adrenals." . . . "That relations exist between the adrenals and infection," urges the same authority, "is today an incontrovertible fact." It follows, therefore, that hypoadrenia from any source should render the body vulnerable to disease. Deficient food, excessive work, that of the sweatshops for example, account for much of the predilection of those subjected to them to disease.

Masturbation and excessive venery are important morbid factors in this connection. The pallor and asthenia witnessed in these cases, so far unexplained, can readily be accounted for if, as I believe, the liquid portion of the semen is rich in adrenal principle. This is suggested by the fact that spermin, the purest of testicular preparations, gives the same tests and acts precisely as does the adrenal principle. The latter is an oxidizing body acting catalytically; it resists all temperatures up to, and even, boiling; it is insoluble in ether and practically insoluble in absolute alcohol, and gives the guaiac, Florence, and other hæmin tests. Now, spermin not only raises the blood-pressure, slows the heart and produces all other physiological effects peculiar to the adrenal principles, but its solubilities are the same; it gives the same tests; it resists boiling. Moreover, it is regarded in Europe as a powerful "oxidizing tonic" and has been found equally useful in disorders in which adrenal preparations had given good results. The inference that spermin consists mainly of the adrenal product suggests that it is not specific to the testes, but, instead, a constituent of the blood at large; not only did this prove to be the case, but it was found in the blood of females as well as in that of males.

[158a] Sézary: Paris médical, Apr. 20, 1912.

[159] Charrin: "Les Défenses Naturelles de l'Organisme," p. 63, Paris, 1898.

Functional Hypoadrenia of Old Age.—Perpetual life would doubtless be ours were it not that all living organic matter is subjected, after more or less precarious periods of growth and adult existence, to one of decline and final disintegration. This applies particularly to the adrenals, if their functions are, as I hold, to sustain oxidation and metabolism, the fundamental processes of the living state. Indeed, the senile state may be said to be as evident in these organs as it is in the features of the aged.

According to Landau,[100] Ecker, Henie, and von Kölliker found that fat occurred in increasing quantities in the adrenal cortex as age advanced, while Hultgren and Andersson found fibrous tissue between the cortex and medulla in very old animals. Minervini[101] found a similar condition in the medulla of aged individuals. Dostojewski, moreover, observed a marked—occasionally very great—reduction in the size of the adrenals in the aged. Rolleston[102] has also called attention to this fact. Landau studied the influence of age on the vessels of the adrenals, adopting for the purpose a process introduced by Rauber and applied by many others, including Bezold, Hyrtl, and Lieberkühn, to the study of other organs, viz., injection of the vessels with some hardening substance, and the subsequent use of a corrosion method to destroy the parenchyma. The adrenals receiving their blood through a number of small arteries, the adrenal vein, which contains no valves, was used for the injection. The annexed plate shows the result. The vessels, and therefore the adrenals, are well developed and in full bloom, as it were, in the adrenals of the three young adults, while those of the aged are shrunken and correspondingly deficient as blood-channels—a certain index of the lowered activity of the adrenal functions, and, through these, of the vital process they sustain.

The asthenia of old age thus finds a normal explanation in the defective supply of adrenal secretion—precisely as it does in Addison's disease. In fact, Rolleston states that atrophy of the glands in the young may produce this disease. Lorand,[103] in

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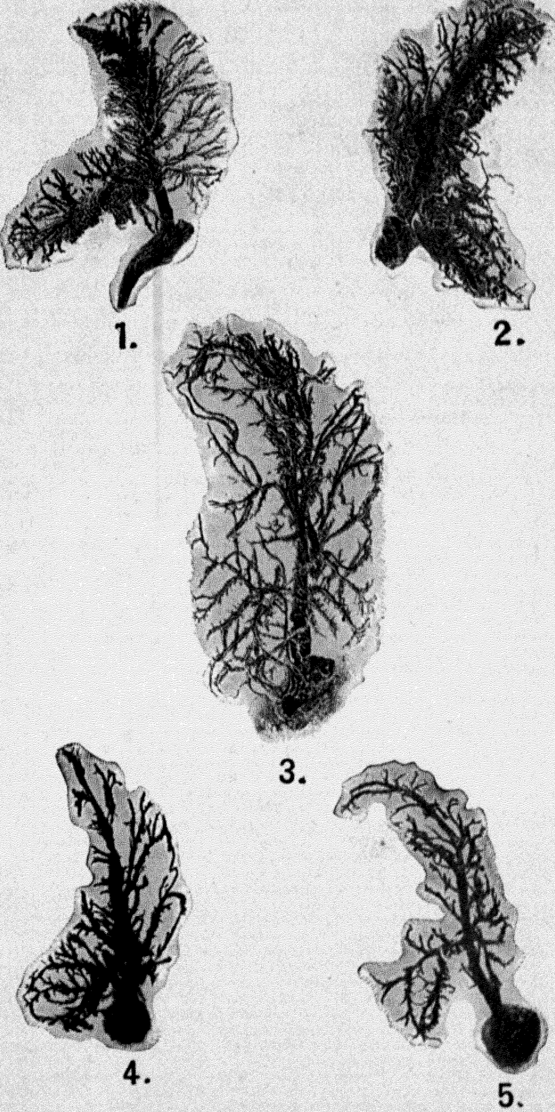
[100] Landau: St Petersb. med. Woch., June 14, 1908.
[101] Minervini: Jour. d'anat. et de physiol., pp. 449 and 639, 1904.
[102] Rolleston: Lancet, Mar. 23, 1895.
[103] Lorand: "Old Age Deferred," Am. ed., p. 111, 1910.



THE ADRENAL VESSELS IN THE YOUNG AND OLD

1, Man 22 years old. 2, Woman 30 years old. 3, Pregnant woman 22 years old. 4, Man 80 years old. 5, Woman 82 years old. (Landau.)

his recently published book on old age, urges in fact that "old age is caused by degeneration of the ductless glands, and that there exists a condition of autointoxication in old age" quite in keeping, I may add, with a decline of the antitoxic power shown by the adrenals. Lorand, who has antedated others in showing the influence of the ductless glands upon old age, has found his views confirmed by Campbell,[164] Pineles, Sir Herman Weber and also—though he denies a relationship between old age and myxœdema—Metchnikoff. We shall see in a succeeding chapter, however, that there exists a close connection between the adrenals and the thyroid in the genesis of old age, in the form of a functional relationship.

In his closing remarks on the causation of old age, Lorand remarks: "It is evident from the above considerations that all hygienic errors, be they errors of diet or any kind of excess, will bring about their own punishment, and that premature old age, or a shortened life, will be the result. In fact it is mainly our fault if we become senile at 60 or 70, and die before 90 or 100." Hence the motto of his title page:—

"Man does not die,
He kills himself."
—*Seneca.*

In the light of the data I have submitted, however, it is clear that the lesions to which the adrenals are subjected during infections and autointoxication, from birth to the last day of life, do greatly to shorten it by limiting the functional area of the organs through the local fibrosis they entail. It is quite probable, in fact, that centenarians owe their prolonged longevity mainly to integrity of their adrenals.

Hygiene, and particularly those of its divisions which bear directly upon the prevention of infectious diseases, thus asserts itself as one of the most useful of our sciences in another direction, viz., that of preserving of organism against those diseases which, seemingly benign because they are recovered from, measles for example, in the end shorten our existence by compromising the integrity of the organs which sustain the vital process itself.

PROPHYLAXIS AND TREATMENT.—Though we are dealing with depraved states of a physiological condition, we cannot but regard them as abnormal in the sense that we deem adynamia abnormal and, therefore, susceptible to remedial measures. Indeed, there is much that can be done in each of the three forms of functional hypoadrenia described.

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[164] Campbell: Lancet, July, 1905.

In *infants*, we should by every possible means prevent infection or intoxication to preserve the integrity of their adrenals and other auto-protective organs. The key of the whole situation lies in the fact that, as Ruhräh states, "nearly all the cases and nearly all the deaths are in bottle-fed babies." Physicians are, as a rule, entirely too ready to yield to the demands of social and other claims put forth by mothers who do not wish to nurse their offsprings. The responsibility assumed by both mother and physician under these circumstances is overlooked. I cannot but hope that if this continues, and the sacrifice of countless infants proceeds, laws may be enacted to prevent it by imposing upon the physician the duty of submitting to the State authorities a certificate in which sound reasons shall alone account for his consent to a departure from Nature's methods which entails deaths untold. J. Lewis Smith states that the death rate among foundlings in New York City reached almost 100 per cent. until wet-nurses were provided. Men such as Jacobi, Winters, and many French authorities have written forcibly upon this subject, but seemingly to no avail. The holocaust continues.

Experimental research in the same direction has only served to emphasize the all-important prophylactic value of maternal milk. As L. T. de M. Sajous[165] states: "That milk is capable of conveying antitoxic substances after these have been injected into the mother has been known for a number of years. In 1892 Ehrlich and Brieger demonstrated this fact in their experiments on mice. The offspring of non-immune mice were suckled by other mice which had been immunized against the actions of certain poisons. It was found that the young were thereby rendered immune to the poisons employed, viz., ricin, abrin, and tetanus toxin. This immunity steadily increased during the period of lactation, persisted for some time after, and then gradually disappeared. Ehrlich thus showed that a passive immunity was created in the young by the absorption of milk from an immune adult, and even went so far as to assert that all so-called hereditary immunity was in reality of the passive variety, being transmitted during lactation and not inherent in the offspring itself.

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[165] L. T. de M. Sajous: Univ. of Penna. Med. Bull., June, 1909.

"This transmitted immunity has been shown to occur in various other animals. Thus, in 1893, Popoff showed that immunity against cholera could be transmitted through cows' milk. He injected bouillon cultures into the peritoneal cavity of a cow and later injected into guinea-pigs from 2 to 10 c.c. of the cow's milk. The guinea-pigs became immune against cholera. The same observer noted also that when the milk was boiled before injecting it no immunity was produced. Kraus showed that the milk of goats immunized by injections of "typhus-coli bacilli" and cholera organisms had protective and agglutinating properties. He also ascertained that the relative proportion of agglutinating substance present in milk to that contained in the serum was as 1 is to 10. Taking up the subject from the standpoint of tuberculosis, Figari showed in 1905 that the agglutinins and antitoxins of this disease appeared in the milk of cows and goats that had been actively immunized against it. In another series of experiments he fed the milk of immune cows to a number of rabbits, and in others injected it subcutaneously. In both cases these animals, thus passively immunized, were found to transmit to their young, by their milk, the agglutinins and antitoxins of tuberculosis.

"Evidence is not lacking of the transmission of antitoxic substances through human milk. It has long been known that infants below one year of age were but slightly susceptible to certain infectious diseases, and in particular scarlet fever, diphtheria, measles, and mumps. In fact, it was in an attempt to throw some light on this subject that Ehrlich performed his classic experiments on mice in 1892. Four years later Schmid and Pflanz performed some interesting experiments on guinea-pigs. Into some of the animals they injected blood-serum derived from human blood which was taken, at the time of delivery of her child, from a woman to whom had been administered diphtheria antitoxin. Into other guinea-pigs they injected milk from the same woman. The animals were then given injections of the ordinarily fatal dose of diphtheria toxin. From the results obtained the investigators concluded (1) that antitoxic substances found in the blood of parturient women exist also in the milk; (2) that the quantity of antitoxic substances excreted with the milk is much less than that found in the blood. Similarly, in 1905, la Torre injected diphtheria antitoxin in several wet-nurses, and noted the antitoxic power resulting in the blood of the nurslings by injecting measured amounts of this blood mixed with diphtheria toxin into guinea-pigs. He was able to satisfy himself that a passage of the antibodies occurred in small amounts into the blood of the infants.

"These experiments show, then, that antibodies injected into the mother are transmitted to the offspring. This being the case, it is but reasonable to expect that some of the protective substances ordinarily present in the normal mother's blood should likewise reach the child through the milk. Experiments have shown this also to occur. Moro found that the bactericidal power of the blood-serum in breast-fed children was distinctly greater than in those artificially fed. Further confirmation was afforded by the fact that this difference rapidly disappeared when the bottle-fed infants were put back to the breast."

The prevention of disease in the infant is raised to its highest standard by maternal lactation. The organisms of its gastrointestinal canal are kept under control; the barriers to infection that the respiratory tract and pulmonary alveoli offer are well armed with antitoxic bodies; the blood itself is destructive to pathogenic organisms, and the infant is thus protected against those diseases which, even if recovered from, we have seen, leave enfeebling lesions, fatty and fibrous degeneration, in those organs upon which his health in after years and the duration of his life depend.

In the *child* beyond the nursling period the problem is more difficult. The fatal "second summer" recalls the sins of the milkman, the filth of the cowshed, and of the vessels in which the milk is transported and kept—amply long enough to favor the growth of the oft-present Shiga bacillus, the virulent bacillus coli, and even at times the streptococcus. The correction of these and many other factors replete with danger to the child, and which surround it on all sides, offers the only resources to diminish not only the mortality of children's diseases, but also their occurrence, besides safeguarding health and longevity in after years. The good already done by our profession in this direction is incalculable. Briefly, public, home, and school hygiene, in the light of the facts I have submitted, not only serves to protect life for the moment when the child is concerned, but its entire career as a healthful individual, while enhancing greatly its chances for a long life.

It now becomes a question whether our resources are such as to enable us to raise, where functional hypoadrenia exists, the autoprotective resources of the child, sufficiently, perhaps, to enable it to resist infection successfully. The influence of many toxins and drugs on the adrenals points clearly to overactivity under their influence. In the first edition of this book, I referred to mercury as occupying "a high position among the stimulants of the adrenal system." Now, C. R. Illingworth[166] and others have found the biniodide of mercury extremely efficient in aborting scarlatina, diphtheria, measles, variola, varicella, pertussis, parotitis, and many other infections. The great vogue of calomel among the physicians of the past generation may have found its *raison d'être* precisely in just such an action—which I have myself observed. Arsenic is a familiar agent in the abortive treatment of malaria in Africa, and, as Surgeon-General Boudin states, in many other diseases. The remarkable results of Petresco with large doses of infusion of digitalis in pneumonia have only been tentatively explained. But if we realize that division of the path to the adrenals arrests and prevents the effects of digitalis, as we shall see elsewhere, there is good ground for the belief that the prevailing conception of the action of this drug is erroneous, and that it is by stimulating the adrenals that it acts, at least in part. In view of the immunizing action of the adrenals, therefore, we can realize how digitalis could be of use in this infectious disease, and how it might prove useful in aborting any pulmonary disorder due to pathogenic organisms. These few examples are submitted merely to show that there is ground for the elaboration of a system of immunizing medication. Its use has served me well.

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[166] Illingworth: "The Abortive Treatment of Specific Febrile Disorders," etc., London. 1888.

Very remarkable in this connection is the action of thyroid gland 1 grain (0.06 Gm.), adrenal gland 2 grains (0.12 Gm.), and Blaud's pill 1 grain (0.06 Gm.) in a capsule three times daily, previously referred to. Given during meals to a debilitated child of 10 or 12 years it seems promptly to start the vital machinery on a new lease of life—where, of course, the demands of hygiene are adequately met. Meat is of value here, while milk, the fluid portion of which gives the test for oxidase, and which, as shown in the second volume, depends upon the adrenal secretion for its ferment (adrenoxidase), is also of great value. Digitalin or strychnine in small doses is added if the heart is weak or to increase the oxygen intake. All these agents tend, by keeping up a slight hyperæmia of the adrenals (and of the other organs acting in conjunction with it), to augment the efficiency of the child's defensive resources.

In the *adult* functional hypoadrenia may have persisted from childhood. Here the measures just suggested for children apply as well not only as preventives where infection threatens, or as abortive treatment, but also to raise the efficiency of the adrenals and the general health of the individual to the normal plane. It is probable that most tonics exert their beneficial influence through the adrenals. That "tonic" doses of mercury, *i.e.*, minute doses, are efficient is well known; we have seen that it is a powerful adrenal stimulant. In toxic doses in fact, as observed by Molinié,[167] it causes intense congestion and even hæmorrhage of the adrenals.

While there is no doubt that meat in excess is harmful, as we shall see under Functional Hyperadrenia, it is no doubt true that, as Lorand[168] states, undernutrition through lack of the necessary proteids in the diet increases the liability to infection, as I urged several years ago in this work. Lorand refers to personal cases of tuberculosis arising from a purely vegetarian diet. On the other hand, Richet and Héricourt[169] obtained remarkable effects from a diet of raw meat in enabling animals to resist tubercle infection by inoculation, and raw meat has become an important factor in the treatment of this disease.

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[167] Molinié: Bulletin général de thérapeutique, Apr. 8, 1906.
[168] Lorand: *Loc. cit.*, p. 313.
[169] Héricourt: Lancet, Jan. 7, 1911.

Grawitz[170] also found that a purely vegetarian diet predisposed to anæmia. We have seen that the adrenals supply the blood its albuminous hæmoglobin, a deficiency of which is an important feature of anæmia. Did we live where pathogenic bacteria do not flourish, we might safely undertake to adopt vegetarian principles; but a reasonable amount of meat, by keeping our autoprotective organs, and particularly the adrenals, active, serves a very useful purpose.

The influence of excessive fatigue on the adrenals, we have seen, is such as to weaken greatly their functional activity and, therefore, their oxygenizing and immunizing functions of the blood. The main harmful feature in this connection is the *relative* deficiency of rest, which means, from my viewpoint, inadequate opportunity afforded the adrenals to recuperate. This, of course, should be proportionate to the amount of strain imposed upon these organs, and the resistance of which they are capable. It is probably owing to lack of this that apparently strong men are often the first to "give out" in forced marches. The physical examination being based mainly upon the *status præsens*, and the adrenals being necessarily (for we are now dealing with a new line of thought) overlooked as factors, there is marked inequality in the resistance of the men to strain. This applies as well to the pathogenesis of chronic disorders. In a personal analysis of 40 cases of hay fever, for instance, the severity of the disease corresponded to a considerable degree with the number of children's diseases the patient had had, the worst cases having had six of these diseases in comparatively quick succession.

This suggests the need of ascertaining the number and severity of children's and other diseases to which the recruit has been subjected and to add this factor to others in deciding upon his admission to the service or the arm to which he is to be assigned. The mounted man suffers less from actual fatigue than the infantryman who must carry his accoutrements, arms, cartridges, etc., aggregating in some armies as much as 70 pounds. When, besides, defective or poor food, impure water, exposure, etc., and other frequent accompaniments of a campaign are taken into account, one need not wonder that disease is a far greater factor as a cause of debility and death than wounds.

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[170] Grawitz: Klinische Pathologie des Blutes, 3d ed., 1906.

Briefly, fatigue should be considered, owing to its inhibiting influence on the adrenals and the immunizing process in which they take part, as an important predisposing cause of disease. The periods of rest should be so adjusted, therefore, as to counteract this by far the most destructive factor of active warfare. In civil life, such hardships are seldom endured, but here likewise much could be done to prevent infection by means calculated to insure the functional integrity of the adrenals.

To stimulate the adrenal functions when marked fatigue prevails would of course only aggravate the hypoadrenia after perhaps a period of temporary betterment. The powdered adrenal substance should, on the other hand, judging from the effects of injections of adrenal extracts in experimentally fatigued animals, serve a useful purpose.

In *old age* the ductless glands assume such importance, that a valuable work has been written by Lorand[171] to indicate how the functional activity of these organs could be preserved in order to retard the ravages of age beyond the fifth decade, while prolonging life. The reader is therefore referred to Dr. Lorand's volume for a mass of information which cannot be considered here.

The adrenals, as shown by the plate opposite page 88, are deficient in circulatory activity, and, therefore, unable to sustain functional activity of all organs up to its former standard. It becomes a question whether, realizing this fact, we should by artificial means excite the adrenals to greater activity. That such a step might shorten life instead of prolonging it is probable. In the first place, the frequent presence of arteriosclerosis in the aged counsels prudence; in the second place, to activate the adrenals would only hasten their degeneration by imposing a greater wear and tear upon them. Drugs capable of enhancing adrenal activity had, therefore, better be avoided in the aged.

Far better is it to *compensate* for the loss of efficiency of the adrenals by supplying to the blood, through a suitable diet, substances which contain the adrenal principle. If my opinion that spermin owes its virtues to the adrenal principle it contains is warranted we can understand why Brown-Séquard rejuvenated himself by means of testicular juice injections (I saw him at the time and can testify to its wonderful effects upon him), since he enriched his blood with the *pabulum* of oxidation, metabolism, and general nutrition, without impairing his adrenals. With advanced knowledge we need not follow his example. We have seen that milk contains the adrenal principle, and that all animal tissues owe their functional activity to its presence. In milk, buttermilk especially (since it is almost pure plasma), we have a ready and inexpensive means to compensate for deficient adrenal activity. If debility and other signs of functional hypoadrenia prevail, I advocate the daily addition to the plain, though varied diet to which elderly people should restrict themselves of the expressed juice (uncooked) of one pound of *fresh* beef daily taken in soup, if distasteful otherwise, and salted to taste. This is a powerful agent for good which is well borne by the stomach, and which more than compensates for the weakened adrenals, since it rapidly restores strength and vigor—provided, of course, harmful influences in other directions are avoided, and a hygienic mode of life, with reasonable out-of-door exercise, prevails.

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[171] A. Lorand: "Old Age Deferred," F. A. Davis Co., Phila., 1910.

In matters sexual, aged men should be extremely reserved, since the waste of seminal fluid to them means waste of life substance replaced with difficulty and never in abundance.

ADDISON'S DISEASE, OR CHRONIC PROGRESSIVE HYPOADRENIA.

That new lines of thought concerning this disease are not untimely is suggested by Anders's previously quoted statement in a recent edition of his textbook that "the pathologic connection between the symptomatic phenomena of Addison's disease and the anatomic lesions has not been made out."

Of major importance in this connection are the facts that advanced lesions have been found in the adrenals post-mortem, though the subject had during life presented no signs of the Addison syndrome, and that, as Davis[172] states, "in the majority of cases the patients have complained of asthenia for a considerable time prior to the appearance of noticeable pigmentation on the surface." Many cases die, in fact, before the pigmentation appears. Under these circumstances it is evident that the prevailing teaching that bronzing is the characteristic sign of Addison's disease—raised to the dignity of a *sine qua non* in some works by the dictum "without bronzing, no Addison's disease"—is an unfortunate one for the patient's welfare, since, as shown elsewhere in this work, bronzing is a symptom denoting advanced lesions of the adrenals or in the course of their secretory nerves, whether in the ganglia or the splanchnic, or even the spinal cord from which the adrenal paths originate. It is because of the presence of these nerves in the abdominal sympathetic (the greater splanchnic in particular, as demonstrated by Biedl[173] and Dreyer[174]), was not known to Martineau,[175] Jaccoud, Lancereaux,[176] von Kahlden,[177] and others that they denied that the adrenal insufficiency was always the underlying cause of the disease, as held by Addison himself, Gull, Trousseau, and many other of the older clinicians. It is apparent that a lesion anywhere in the course of these nerves must be capable of causing inhibition of the adrenal functions and Addison's disease, by interfering both with the secretory activity of the glands and the formation of their secretion. This is well exemplified by cases reported by Semmola and Brault in which bronzing was due to pressure upon the semilunar ganglia and the solar plexus; the flow of impulses through these structures to the adrenals being impeded, the functions of these organs were inhibited. Pressure or organic lesions may occur anywhere in the pituitaro-adrenal nerve-path. Even the cachetic stage of acromegaly is often attended by a bronze pigment "strongly resembling that found in Addison's disease" we have seen. From my viewpoint, therefore,

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[172] Davis: Sajous's Cyclopædia of Prac. Med., vol. I, p. 123, 2d ed., 1900.

Addison's disease is the symptom-complex of progressive hypoadrenia, i.e., *of insufficiency of the adrenals. It occurs when, owing to progressive organic lesions in these organs or in the course of their secretory nerves (the abdominal sympathetic and its ganglia, the spinal axis or the pituitary body), the*

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[173] Biedl: *Loc. cit.*
[174] Dreyer: *Loc. cit.*
[175] Martineau: Thèse de Paris, 1864.
[176] Lancereaux: Archives de Medecine, Jan., 1890.
[177] Von Kahlden: Archiv f. Anat. u. Phys., Bd. cxiv.

adrenal secretion produced is increasingly inadequate to sustain general oxygenation, metabolism and nutrition, and the cardiovascular tone.

PATHOGENESIS AND SYMPTOMATOLOGY.—These will be considered together to indicate the intimate relationship between them when the functions of the adrenals are interpreted from my viewpoint. This will be further facilitated by analyzing the symptoms in their physiological sequence.

Hypothermia, Coldness, and Dyspnœa.—These symptoms are self-evident results of deficient oxygen intake, and of the correspondingly deficient oxidation and metabolism incident upon the deficiency of adrenal secretion. The sensation of cold is aggravated by the fact that the deficiency of the latter—or rather of the adrenoxidase it becomes—entails relaxation of the arteries and a low blood-pressure; the blood accumulating in the larger trunks of the splanchnic area, the peripheral vessels are partially depleted of theirs, and peripheral oxidation being thus diminished from two directions, the patient complains of chilliness. The dyspnœa is due to the same two factors: inadequacy of adrenal secretion to properly oxygenize the blood, and ischæmia of the lungs through retrocession of the blood into the deeper vessels. An aggravating factor is the intense muscular weakness which also, of course, affects the thoracic respiratory muscles.

Progressive Asthenia, Weak Heart Action, and Vascular Hypotension.—Oliver and Schäfer and, later, Cybulsky and Szymonowicz having found, we have seen, that the adrenal secretion sustained the tone of the cardiovascular and skeletal muscles by a direct action upon them, a process supplemented, as I have shown, by its power to sustain oxidation and metabolism in these (as well as all other tissues), it is obvious that deficiency of this secretion should produce weakness of all muscular tissues, *i.e.*, loss of contractile power. Asthenia, weak heart action, and relaxation of the arteries—the blood-pressure sometimes being as low as 50 mm.—are thus a direct result of the adrenal insufficiency. Here again, however, the low vascular tension aggravates the morbid process by causing retrogression of the blood toward the deeper channels of the splanchnic area. The cardiac and skeletal muscles receiving an unusually small volume of blood, their contractile power is weakened in proportion and their resistance to fatigue reduced practically to *nil.* Sergent has proposed a diagnostic sign, "the white line," which I would explain by this peripheral ischæmia, is obtained by lightly rubbing the surface of the abdomen with the pulp of a finger. A broad, white streak soon appears, which gradually becomes more distinct, then after three or four minutes fades away.

Emaciation, Anorexia, Vomiting, Diarrhœa.—That deficient oxidation and metabolism, upon which nutrition depend, should entail emaciation is self-evident. Anorexia is but a consequence of this state of affairs, the utilization of less foodstuffs being a normal result of deficient demand for the same by the tissues. The vomiting is due mainly to the gastroptosis caused by relaxation of the muscular coat of the stomach, a condition similar to that present in all other muscles of the body. Vomiting occurs when imperfectly digested materials accumulate in the stomach, partly because of its dilatation and partly as a result of deficient peristaltic action from the same muscular incompetence. A corresponding degree of asthenia of intestinal muscles also entails constipation owing to deficient peristalsis in certain cases, while in others, or subsequently, there is diarrhœa owing to relaxation of the intestinal arterioles and the resulting passive congestion of the intestinal mucosa.

Bronzing.—Langlois, Gourfein, and others have found that one-eleventh of the adrenals sufficed to carry on their functions; this illustrates the small proportion of adrenal secretion required and the progress any local lesion may make before the organism at large is morbidly influenced. Vassale and Zanfrognini[178] found that if all but a small fraction of the medulla is left in experimental animals, all the typical signs other than pigmentation may appear. This illustrates the valuelessness of Nothnagel's observation that pigmentation did not occur in 153 animals from which he had removed both adrenals. Death occurred in all these animals long before bronzing had had time to occur. Boinet, who, on the other hand, utilized rats, which are known to survive the operation longer than any other animal—owing to the frequent presence of accessory organs—observed typical pigmentation in all animals which had had several months' postoperative life. Tizzoni noted similar results after crushing the organs; Brown-Séquard, in fact, had long before noted that bronzing appeared in animals in which the operation did not prove fatal for some months, the other symptoms present being analogous to those of Addison's disease. It is because of these and other facts adduced in the earlier editions of this work that I concluded[179] that "*insufficiency of the adrenals only manifests itself by bronzing when, from any cause, all but a small proportion of the organs has been rendered physiologically inactive.*" Briefly, the bronzing of Addison's disease occurs only in advanced hypoadrenia.

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[178] Vassale and Zanfrognini: Riforma Medica, Oct. 31, 1902.

We have seen that the pigment which gives the skin and the mucous membranes their bronze hue is mainly composed of the adrenal product, or adrenoxidase, which, from my viewpoint, is the oxidizing body of the hæmoglobin.[180] That the pigment was a product of the adrenals was first suggested by Brown-Séquard. But why should it, though a constituent of the circulating blood, accumulate in the tissues? Here, again, two factors prevail: the extremely weak blood-pressure in advanced cases, and the identity of the adrenal product as the albuminous constituent of hæmoglobin. The *vis a tergo* motion of the blood being slowed, the plasma circulating in the cutaneous capillaries is increasingly unable to traverse these minute vessels and is deposited in the rete mucosum. The adrenal constituent being freed, it resumes its original reducing power and undergoes the changes of color witnessed when fluid-extracts of adrenal substance are exposed to the air and light—a yellowish brown gradually turning to bronze and often to black. It is because of this that bronzing is not characteristic of Addison's disease, and that it occurs in other cachectic disorders.

This does not militate against the production of bronzing by other factors, local irritation, drugs, cutaneous or nervous disorders. It explains only its mode of production in Addison's disease, as I interpret it.

Lumbar and abdominal pain often occurs early in the isease, but may be absent through its entire course. The fact hat it occurs suddenly in crises points to pressure upon the abundant nervous structures in the immediate neighborhood of the adrenals or through dilatation of these organs when the general blood-pressure, from any intercurrent cause, becomes high. The intense congestion attending or preceding adrenal hæmorrhage, which often terminates Addison's disease, suggests that a temporary exacerbation of the local hyperæmia incident upon the local lesion is the main cause of this symptom.

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[179] See 1st, 2d, or 3d ed., p. [illegible].
[180] This question is treated in full on p. [illegible].

Tendency to Syncope, Impairment of Vision, and Hearing.—The tendency to syncope is such in some cases that elevation of the head sometimes suffices to cause death. Not only is this accounted for by the low blood-pressure and the resulting cerebral ischæmia, but also by the poverty of the blood in adrenoxidase, its oxidizing principle. The extremely small, soft, compressible, and sometimes imperceptible pulse bespeaks a third factor in the pathogenesis of this symptom: great systolic weakness of the heart, owing to loss of the direct support received from the adrenal secretion in transit through its right auricle and ventricle, and deficient metabolism in the left myocardium.

The same cerebral ischæmia and anæmia which predispose to syncope and vertigo also affect the organs of special sense; hence the impaired vision and hearing.

Headache, Irritability, Hallucinations, Delirium, Convulsions.—We have seen that, as shown by Abelous and Langlois, the adrenal secretion is endowed with antitoxic functions. It follows, therefore, that any adrenal disorder capable of materially reducing the supply of this secretion must lead to accumulation of the tissue poisons it is known to destroy. It is these poisons that give rise to headache, irritability, muscular twitching, rigidity, delirium, and convulsions similar to those witnessed in puerperal eclampsia, also due to endogenous poisons.

Coma, Sudden Death.—Gradual decline with profound asthenia, or some intercurrent disorder and coma often terminates the case, but not infrequently death occurs in the midst of a convulsion, or suddenly without such, owing to adrenal hæmorrhage. This is due to the accumulation of poisons referred to under the preceding heading. By irritating or exciting the vasomotor center, these poisons cause a rise of blood-pressure and even fever. The remnant of medulla in the adrenals and their intrinsic sinusoidal vessels, medullar and cortical, being subjected to inordinate pressure, suddenly rupture, constituting what Arnaud has very aptly termed "adrenal apoplexy."

Treatment.—The only curative measure worthy of any confidence is one calculated to replace the destroyed glands or, at least, to supply the organism with the adrenal product in some form.

The grafting of adrenals into the tissue has led to such unfortunate results that Courmont, after a personal experience in the use of this procedure, declared it formally contraindicated. Indeed, Bra,[181] after grafting the suprarenals of a dog into the cellular tissue of the abdomen in a child of 14 years, witnessed its death in three days. Jaboulay,[182] having resorted to the same method in two cases, lost both within twenty-four hours, owing, he honestly admits, to the operation. The same result followed in Courmont's case. If this question is closely analyzed, however, it becomes apparent that it is not the method proper, or the operators, that are responsible for the untoward results, but rather the fact that the functions of the adrenals were still too obscure, at the time the operations were performed, to afford the indications necessary for a judicious adjustment of the quantity of adrenal tissue grafted to the needs of each particular case.

The cause of death in such cases is made clear by my interpretation of the functions of the adrenals. Thus Courmont, referring to the three cases in which dog's adrenals had been grafted in cases of Addison's disease, writes: "In the three cases the results were disastrous. In my own case the patient died in twenty-four hours with a *formidable hyperthermia* and cardiac collapse," while specifying that there was no infection of the wound. With the adrenals as the source of a secretion whose mission is to sustain oxidation, the cause of the excessive temperature is self-evident. The grafted adrenal tissues furnished adrenal substance far in excess of the needs of the organism, and the phenomena produced were those of the physiological function carried out by the secretion, but "formidably" exaggerated.

If grafting is resorted to, the proportion of tissue employed should be adjusted to the needs of each case, always beginning with a small quantity of tissue and adding small grafts until distinct improvement is noted. It must be said, however, that the experimental use of small grafts has not, so far, been attended with much success.

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[181] Bra: Cited by H. X. Adams, Practitioner, Oct., 1902.
[182] Jaboulay: Lyon Médical, Mar. 31, 1897.

Indeed, it has not been possible to obtain successful grafts in a sufficiently large proportion of experimental animals so far to warrant grafting in man. Dominicis,[183] Boinet, Imbert,[184] Coenen,[185] Taddei and Torrini,[186] and others had unsuccessfully attempted to introduce grafts in various parts of the body. Abelous,[187] however, succeeded in preserving life in animals from which the adrenals had been removed by means of grafts; but subsequent degeneration of the latter caused death. Gourfein met with similar results. Haberer,[188] after partly detaching one adrenal in such a way as to provide a pedicle which would continue to supply the organ with blood, inserted the free segment in a slit in the kidney. This operation, tried in 86 animals, proved successful in 50 per cent. But to replace a diseased organ, transplantation of a normal organ obtained from another subject or lower animal is necessary. The nearest approach to this result was that obtained by Busch, Leonard, and Wright,[189] who succeeded in transplanting the adrenal of one rabbit into the kidney of another which had also been deprived of one adrenal. On removing the remaining adrenal thirty-six days later, the animal recovered, showing that the implanted adrenal was functionally active. On removing the kidney containing the grafted adrenal twenty-nine days later, however, the animal died in forty-three hours. On the whole, it has become apparent that the kidney is the best structure for the implantation of adrenal grafts, and that it is in this direction that our attempts at grafting should be directed. Recalling the experience of Jaboulay, Courmont, and others to the effect that the dog's adrenal produces fatal hyperthermia, the organs of smaller animals might be used, adding one or more subsequently if need be.

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[183] Dominicis: Gazetta degli Osp. e. d. Clin., Nov. 22, 1896.
[184] Imbert: Le Bulletin Médical, Nov. 8, 1899.
[185] Coenen: Arch. f. klin. Chir., B. lxxxi, Hft. 2, 1907.
[186] Taddei and Torrini: Lo Sperimentale, July-Aug., 1907.
[187] Abelous: C. R. de la Soc. de Biol., Nov., 1892.
[188] Haberer: Arch. für klin. Chir., B. lxviii, No. 2, 1908.
[189] Busch, Leonard, and Wright: Jour. Amer. Med. Assoc., Aug. 22, 1908.

As to the general results of adrenal preparations and grafting, a series of 120 cases collected from literature within my reach, including 97 previously collected by E. W. Adams,[190] in all of which adrenal preparations had been used in some form, gave the following results:—

1. Cases in which death can be ascribed to grafting or adrenal preparations	8
2. Cases in which the benefit was slight or nil	51
3. Cases in which marked improvement occurred	36
4. Cases in which permanent benefit was obtained ..	25
	120

The unfavorable results obtained with adrenal preparations given orally are doubtless due, in a great measure, to their empirical use, and regardless of the dose indicated in each case. E. W. Adams[191] refers to a group of 7 cases, "in which alarming or fatal results were presumably or possibly due to the treatment." He mentions, for instance, 2 cases reported by Affleck[192] treated with "suprarenal gland extract." The chart notes include the words: "Alarming collapse. One of the cases began to improve markedly when the extract was stopped." In the original paper, reference is made to another case treated by suprarenal extract in which "similar collapse was noted." The dose was not mentioned. Such cases are apt to be regarded as examples of the sudden death observed in Addison's disease, to which Addison himself, Dieulafoy, Anderson, Bradbury, and others have called attention. Guiol,[193] having observed similar signs of intoxication and collapse, tried the remedy in a normal subject and obtained the same morbid phenomena. The essential feature in carrying out this mode of treatment is to *adjust the amount administered* to the *needs of each case.* Addison's disease being due, from my viewpoint, to inadequate oxygenation and metabolic activity, the results in turn of a deficient production of the adrenal secretion, it follows that *the temperature and blood-pressure indicate the*

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[190] Adams: Practitioner, Oct., 1903.
[191] Adams: *Loc. cit.*
[192] Affleck: Lancet, Dec. 31, 1898.
[193] Guiol: Bull. de la Soc. médico-chi. du Var, Dec., 1906.

degree to which the adrenals are still performing their functions. It is plain, therefore, that our aim should be *to supply only just enough adrenal extractive to compensate for the deficiency of adrenal secretion produced.*

This may be illustrated by the history of 25 cases of Addison's disease in which, out of the 120, permanent benefit occurred. In 1 of these, treated by Bate,[194] but 1/12 grain (0.005 Gm.) of adrenal extract three times daily caused very great and lasting improvement with marked lessening of the bronzing. When the remedy could not be obtained temporarily, which occurred twice, the case relapsed. Conversely, Suckling[195] began with 10 grains daily in another case and gradually increased until 175 grains were given each day; he also obtained favorable results. That in Bate's case the adrenals were still able *almost* to carry on their function is self-evident, while in Suckling's the remedy practically compensated for the adrenals; the local morbid process in them was still active, and such as to paralyze their functions—a fact which was well shown by the severity of the case when the use of the extract was begun. The average dose is probably that used by Weigall[196] in a very severe case—5 grains, increased to 10 grains, of the extract three times a day. The patient increased 6 pounds in two weeks, and after about three months 56 pounds. In other words, in the 25 cases of permanent benefit, although the remedy was used empirically, it so happened in all probability that *the doses employed coincided with the needs of the organism.* In the 51 cases in which no benefit was obtained several occur in which failure was evidently due to inadequate dosage or to too early cessation of the treatment, while in others excessive doses—practically in every instance a too rapid or excessive increase of the dose—as clearly prevented a successful issue.

Excessive doses may not only raise the temperature beyond normal, as we have seen, but they may also, by increasing general oxidation and metabolism, so increase the functions of the thyroid that we may have, besides, symptoms of exophthalmic goiter. Boinet[197] reported such a case in a patient who had increased the dose of his own accord. The same clinician[108] observed sudden death in 2 cases after injecting 1/180 grain of adrenalin, the rise of pressure having produced, doubtless, hæmorrhagic destruction of what remained of adrenal medulla.

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[194] Bate: Amer. Pract. and News, Aug. 1, 1899.
[195] Suckling: Brit. Med. Jour., May 28, 1898.
[196] Weigall: Australasian Med. Gaz., Oct. 20, 1905.
[197] Boinet: C. R. de la société de biol., p. 891, 1899.

Desiccated suprarenal gland, provided a good and fresh preparation is used, is the most effective agent now at our disposal. It was first used by Abelous, Charrin and Langlois, of Paris, and has also been found efficient by Sergent,[109] Hirtz and Debré,[109a] and others. Judson Daland[109b] reported a case due to adrenal tuberculosis in which suprarenal increased greatly the vitality and strength without greatly increasing the blood-pressure. The tubercular process should be treated simultaneously.

The preparation now generally employed, the dried gland (the *glandulæ suprarenales siccæ* of the U. S. P.) is available in tablet form, 1 grain representing about 5 grains of the fresh gland. If the blood-pressure and the temperature are considerably below normal, 3 grains (0.2 Gm.) may be given to an adult twice daily during meals from the start, and kept up and increased if need be until they become normal, regulating the dose thereafter so as to maintain this level. Smaller doses are indicated if the blood-pressure and temperature do not depart much from the normal. The powder is sometimes to be preferred in the same doses, owing to the possibility of administering it in capsules which conceal the rather unpleasant odor of adrenal gland.

Glycerin extract of fresh gland may be prepared where the desiccated gland cannot be obtained; or the fresh mutton or beef gland may be given twice daily, in doses of 5 to 15 grains, with the food. The glycerin extract is also used hypodermically, but the injections are painful and are no more effective than the dried gland.

As previously stated, I ascribe the therapeutic effects of pituitary extract to the adrenal principle it contains. It is indicated, therefore, in Addison's disease. The best way to administer it is by intramuscular injections, using 15 minims (1 c.c.) of the preparation termed "vaporole" by Burroughs Wellcome and Co. and supplied in small vials containing the above quantity. The dose should be renewed as frequently as needed to raise the temperature to normal and keep it there.

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[108] Boinet: Arch. générales de méd., Feb. 9, 1904.
[109] Sergent: Jour. de méd. et de chir. prat., June 10, 1912.
[109a] Hirtz and Debré: Paris Méd., June 27, 1914.
[109b] Daland: Endocrinology, July-Sept., 1918.

Pitres and Gautrelet[200] found recently that the use of glucose, to compensate for the deficient formation of glycogen (due to inadequate conversion of starches into this substance), caused the intense adynamia and sensation of fatigue to improve materially, especially when given simultaneously with adrenal preparations.

Iron in the form of Blaud's mass is of advantage to counteract the anæmia. The adrenal product, by increasing the albuminous hæmoglobin, requires the iron to build up hæmatin and the complete hæmoglobin. It is indicated even when the blood-count, which may be very low, as noted by Hayem, shows but little diminution of red corpuscles. One grain of iron can be given with desiccated adrenal powder in capsules. Other drugs should be used with great circumspection, especially in advanced cases. Strychnine, digitalis, and other drugs which raise the blood-pressure expose the patient to adrenal hæmorrhage.

The intense asthenia, the tendency to syncope on exertion, and the weakness of the heart impose the need of remaining as quiet as possible. When the case is advanced, rest in bed is indicated. Nutritious, but readily digested food tends to delay the morbid process, meats and milk contributing their own adrenal substance to compensate in a measure for the patient's inadequate supply. Lavage of the stomach affords considerable relief in cases in which there is gastroptosis and retention of food materials as a result of relaxation of the muscular coat of the stomach, in keeping with the adynamia of all muscular elements. Bismuth is the safest agent to use for the diarrhœa in conjunction with the adrenal preparation employed.

When Addison's disease is due to tuberculosis of the adrenals, as is usually the case, the carbonate of creosote 5 grains (0.3 Gm.) three times daily may advantageously be given with the adrenal preparation. The iodides, which do not raise the blood-pressure, have been used with advantage.

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[200] Pitres and Gautrelet: Revue de Thérap. Médico-Chir., Aug. 15, 1912.

TERMINAL HYPOADRENIA.

For reasons given on page 80, the term "hypoadrenia" was introduced in lieu of those at present in vogue, which are either incorrect or cumbersome. Interpreted from my viewpoint,

Terminal hypoadrenia is that form of adrenal insufficiency which occurs late in the course of an acute febrile disease, as a result of the exhausting secretory activity, probably aggravated by temporary local lesions to which the adrenals are subjected, as defensive organs, during the febrile period of the disease. It should be clearly differentiated from intercurrent *hyper*adrenia, a more dangerous type, considered beyond, which may appear at any time in the course of an acute infection or toxæmia.

The adrenals being admittedly concerned in the protection of the organism during infections and intoxications by contributing an excess of their secretion during the febrile stage of the disease (sometimes considerably prolonged), it follows that after this stage is over the adrenals should lapse into a condition of more or less temporary insufficiency through fatigue or exhaustion. This effect is well exemplified by the recent observation of Carl[201a] that the adrenals of frogs after strychnine convulsion and also of a bicyclist who had died of extreme exertion no longer gave the chromaffin reaction.

In lobar pneumonia and bronchopneumonia, for instance, resolution may be considerably delayed and convalescence likewise. There is, late in the case, extreme adynamia and a low blood-pressure, the temperature is below normal, the pulse weak and more or less rapid, and death from heart-failure is not infrequent. In typhoid fever, hypoadrenia is commonly observed. The disease assumes what is now known as the cardiac type, with weak pulse, prostration, a tendency to fainting. A case of this class, and which shows clearly the adrenal involvement, was recently described by Josué.[201] Here, again, we find, late in the case, extreme prostration, a rapid, weak and sometimes irregular pulse, hypothermia, and a marked tendency to vertigo, fainting, and cardiac failure. Are these phenomena due, in keeping with the effects of poisons on the adrenals already described in these pages, to vascular lesions of these organs? Sicard[202] reported the case of a young woman in whom the foregoing symptoms appeared on the ninth day of a bronchopneumonia. Extreme muscular weakness, marked hypothermia and low blood-pressure, diarrhœa, and Sergent's white line were present. On the fifteenth day the blood-pressure fell to 70 or 80 (7 or 8 per cent. Potain) and death followed three days later. At the autopsy the adrenals were found hæmorrhagic. This suggests that adrenal lesions may be present in all such cases. Yet, Ribadeau-Dumas and Bing[203] have witnessed the same symptoms in cases of measles which recovered, while Bossuet[204] refers to 8 cases in various febrile disorders in which typical symptoms of adrenal insufficiency, asthenia, low blood-pressure, etc., developed suddenly and disappeared spontaneously, aided perhaps by adrenal extract which had been administered. What organic lesions occur in such cases, therefore, are not necessarily fatal, as emphasized by the areas of fibrosis (old healed lesions) often found at autopsies.[205]

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[201] Josué: Société Médicale des Hôpitaux, May 21, 1909.
[201a] Berliner klin. Wochenschrift, June 12, 1911.

As well stated by Morichau-Beauchant,[206] the adrenals seem to show a special predilection for certain infections. Diphtheria easily leads them all in this connection. So seriously do these organs suffer in these cases that Sevestre and Marfan have termed the type "secondary syndrome of malignant diphtheria." Hutinel ascribes the fulminating cases of scarlatina to this cause. Tetanus, erysipelas, mumps, certain forms of tonsillitis, and certain streptococcic infections are occasionally witnessed which also present the typical syndrome of hypoadrenia. Goldzicher[207] was led by his researches to conclude that in the various forms of septicæmia the appearance of lower blood-pressure was to be ascribed to insufficiency of the adrenals. Finally, Comessatti[207a] found that in diseases of long duration, the adrenalin contained in the adrenals was far less than in those of subjects in which death had occurred suddenly.

PATHOGENESIS AND SYMPTOMATOLOGY.—These two features of terminal hypoadrenia have been partially covered in the foregoing lines. Briefly, if at the end of an infectious disease the case, instead of proceeding to convalescence, remains in a condition of asthenia, with low blood-pressure and temperature, there is good ground for the conclusion that this form of hypoadrenia has occurred. Exhaustion of the adrenals during the acute process having inhibited their secretory activity, the above symptoms result from inadequate oxidation of, and metabolic activity in, the tissues. Sergent's white line, already described, may be obtained in the majority of these cases. The patient complains of chilliness, the surface is pale owing to the poverty of the blood in cellular elements and hæmoglobin, and to recession of the blood-mass from the surface to the deeper vascular trunks. The vascular tension being low the pulse is rapid and the heart-beat weak. Anorexia due to deficient metabolism and diminished nutritional needs, nausea, the result of relaxation of the gastric muscular coat, and diarrhœa due to a similar condition of the muscular coat of the (already passively engorged) intestine, more or less frequent fainting spells may all be witnessed in such cases, which are always greatly exposed to relapse or to sudden demise from heart-failure.

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[202] Sicard: Bulletin de la Soc. Médicale, July 21, 1904.

[203] Ribadeau-Dumas and Bing: Bull. de la Soc. Anat., June 3, 1904.

[204] Bossuet: Gazette hebd. des Sc. méd. de Bordeaux, Oct. 30, 1904.

[205] Loeper and Oppenheim, in Malad. des Reins et des Caps. Sur., by Debove, etc., p. 738, 1906.

[206] Morichau-Beauchant: Le progrès médical, Oct. 9, 1909.

[207] Goldzicher: Wiener klin. Woch., June 10, 1910.

[207a] Comessatti: La Clinica med. Italiana, Nov., 1910.

Complications of various kinds may occur. The immunizing processes being greatly weakened through the deficiency of adrenal secretion, one of its important factors, septic infection, abscesses, bone lesions, tuberculosis of a rapid type, and other infections may more or less rapidly develop. Disorders of nutrition, cholelithiasis, and occasionally Addison's disease may also appear. In acute pulmonary infections, pneumonia, for example, tissues in the neighborhood of the focus of infection, the pleura, the heart, etc., inadequately protected by the blood or its phagocytic cells become infected. Briefly, the body is rendered vulnerable to the attacks of almost any pathogenic organism.

Pathology.—In the special type in question no adrenal lesion may be discernible. In the majority of instances, however, the organs are enlarged and congested, and may show here and there a limited hæmorrhagic area. Their appearance suggests not only the conditions incident upon functional exhaustion, but the presence of a *passive* congestion (see page 34) resulting from loss of resiliency of their sinusoidal vessels, thus impeding the circulation through them. Occasionally they are the seat of suppuration, a complication which is apt to be observed when the causative disease is, or includes, a streptococcic infection, pneumonia or meningitis.

The pathological picture of the more severe form of adrenal complication, *i.e.*, intercurrent hyperadrenia, considered beyond, shows far more distinct lesions of the adrenal parenchyma. Hence the typical lethal phenomena that attend many of these cases.

TREATMENT.—In these particular cases opotherapy, or rather the use of adrenal gland, or of pituitary body, which acts very similarly, but with less violence and more lasting effects, sometimes gives surprising results. The adrenal product—which from my viewpoint is also the main active agent in the neural lobe of the pituitary, as shown by the chromaffin test—supplies precisely what the body needs, *e.g.*, the resumption of all oxidation processes, which means general metabolism and nutrition, and the resulting rise of blood-pressure, which causes the blood to circulate normally in all organs, including the skin, and in the adrenals themselves. Indirect effects are also obtained: its action on the heart increases the contractile power of this organ, and, being thus rendered capable of projecting the blood with more vigor through the lungs, oxygenation of the blood becomes more perfect—a process materially aided by the rise of blood-pressure, which, as stated, drives the blood from the splanchnic area toward the peripheral organs, including the lungs and the brain. From these features alone, considerable benefit is derived. If we recall, moreover, the participation of the adrenal secretion (which the adrenal preparation administered represents) in the immunizing process, we have the added factors of ridding the blood of any intermediate—and therefore toxic—wastes, bacterial toxins, etc., it may contain, and of increasing phagocytic activity, thus antagonizing efficiently any pathogenic organism that may remain to compromise the issue. Thus explained, we can understand the phrase "little short of marvelous" applied to the results obtained by some clinicians. We can also understand the marked reduction in the mortality obtained by Hoddick[208] in cases of peritonitis following appendicitis accompanied by uncontrollable decline of the blood-pressure, cyanosis, and other evidences of collapse, and also in puerperal toxæmias, by the slow intravenous use of adrenalin in saline solution. Hoddick ascribes the lowering of the blood-pressure to paralysis of the vasomotor center; but as the toxæmia is the cause of this condition, an agent capable of counteracting both cause and effect is necessary. This is met by the adrenal principle. Josué,[209] in typhoid fever, likewise relieved threatening symptoms by injecting 15 minims (1 c.c.) of adrenalin (1 : 1000 sol.) in ½ to 1 pint (250 to 500 c.c.) of physiological saline solution subcutaneously. The influence of the saline solution in these cases must not be overlooked, however. Seven years ago, I urged that death was often due, in infectious and septic diseases, to deficient circulatory osmosis, and advised the use of saline solution *from the onset* in all febrile diseases. Netter[210] has used large doses of the adrenal active principle with profit. Marran and Darré[211] found it of great value in the collapse of diphtheria with marked asthenia, low blood-pressure, and subnormal temperature. Moizard[212] recommended adrenal opotherapy as soon as asthenia and low blood-pressure occur in any infection. He gives daily two fresh adrenals from the sheep, finely divided and mixed with powdered sugar, or, better, the use of the active principle, adrenalin, supracapsulin, etc., 10 to 20 drops daily divided in five or six doses. Kirchheimer[213] has found large doses (10 to 24 minims) safe hypodermically in the collapse of pneumonia, diphtheria, and scarlet fever. Letulle, Lemoine, Grysez, and Dupuich[213a] have found it of great value in the latter disease. Lesné, Gérard, and Francon[213b] noted that the sudden death in erysipelas showed the characteristic symptoms of adrenal inhibition and obtained good results from the internal use of adrenalin and digitalis. The better plan, from my viewpoint, is to inject adrenalin with saline solution (at 108° F.) intravenously.

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[208] Hoddick: Centralbl. f. Chir., Oct. 12, 1907.
[209] Josué: *Loc. cit.*
[210] Netter: Soc. Médicale des Hôpitaux, May 7, 1909.
[211] Marran and Darré: Journal des praticiens, May 15, 1909.
[212] Moizard: Revue de thérapeutique, Jan. 1, 1910.
[213] Kirchheimer: Münch. med. Woch., Dec. 20, 1910.
[213a] Lemoine, Grysez, and Dupuich: Bulletin médical, Jan. 17, 1912.
[213b] Lesné, Gérard, and Francon: Presse médicale, Nov. 15, 1911.

These measures are only indicated in emergency cases, however. In the average case the *glandulæ suprarenales siccæ* of the U. S. P. administered by the mouth is fully as effective if a good preparation is obtained as soon as asthenia and low blood-pressure appear. The powder in 3-grain (0.2-Gm.) doses three times daily in capsules, gradually increased until 5 grains are given at each dose, usually suffices. When the cardiac adynamia disappears, a small dose of thyroid, the desiccated gland, also ½ grain (0.03 Gm.) strychnine 1/60 grain (0.001 Gm.) and Blaud's pill, 1 grain (0.06 Gm.) added to each capsule greatly hastens convalescence. The iron and the adrenal product serve jointly to build up the hæmoglobin molecule, a slow process when left to itself.

For our knowledge of the action of the use of pituitary extracts in infectious diseases we are mainly indebted to L. Rénon and Delille,[214] who began their use in 1907. In a recent work in which the observations of both observers are recorded, Delille,[215] referring to grave cases of typhoid fever, states that they showed "arterial hypotension, irregularity of the pulse (especially the grave forms), oliguria, insomnia; while convalescents showed asthenia, hypotension, or at least effort hypotension (Oddo and M. Achard), paroxysmal or continuous tachycardia"—all, we have seen, symptoms of hypoadrenia. They found 1½ grains of pituitary extract (of both lobes), at noon daily, extremely efficient; it counteracted at once the depressed arterial tension, produced diuresis, relieved the insomnia, and greatly improved the general condition. Similar effects were observed in diphtheria and erysipelas. The use of the pituitary extract "vaporole," as described under the preceding heading, is also indicated in these cases. The results in pneumonia do not appear to me to warrant the use of any adrenal or pituitary preparations early in the case, the first few days of the disease, when the blood-pressure and the fever are high. They should be used *only when a low blood-pressure and other symptoms of hypoadrenia are present.* The results reported by Delille strengthen this opinion. In advanced tuberculosis no beneficial effect was observed.

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[214] Rénon and Delille: Bulletin de thérapeutique, Feb. 8, 1907.

[215] Delille: "L'Hypophyse et la Médication Hypophysaire," 1909.

HYPERADRENIA.

Just as "hypoadrenia" has seemed to me to replace advantageously both "adrenal insufficiency" and "hypoadrenalism," so does "hyperadrenia" appear to convey a more exact meaning of excessive adrenal activity than "hyperadrenalism," which suggests the presence of habitual overactivity, and to be less cumbersome than the phrase "excessive secretory activity" and others habitually used.

To recall briefly the effects of large doses of adrenal extract, is all that is necessary in the present connection. Textbooks merely refer to the fact that it causes marked slowing of the heart, marked constriction of the blood-vessels, and a decided rise of blood-pressure; but we would not proceed far with these archaic limitations were we to attempt to explain with them the phenomena included under hyperadrenia. I shall, therefore, continue to have the interpretation of the phenomena witnessed upon the conception of adrenal functions I have advanced, viz., that the adrenals supply a secretion which becomes converted in the lungs into the oxygenizing albuminous constituent of the hæmoglobin molecule, and that as such it governs metabolism and nutrition, the action on the heart and blood-vessels being but an incidental result of this function. We have seen also that the adrenal secretion took part in the immunizing processes of the body at large. We shall now find that these functions account for those of hypoadrenia, as they did under the preceding heading.

Were we to identify a "functional" type, as I did in the opposite condition, hypoadrenia, we should find it necessary to include the many conditions in which overactivity of the adrenals takes an important part. When we recall, however, that, from my viewpoint, these organs play a leading rôle in all febrile affections, that an excess of adrenal secretion in the blood means hyperoxidation and hyperactivity of all organs, and that as a result we may have glycosuria, psychoses, pulmonary œdema, and many other symptoms, it will become apparent that no such a "functional" type could well be proposed without endowing the adrenals with a great part of the whole field of pathology. It was deemed far preferable, therefore, to treat known diseases in the usual way and to illustrate the rôle played in their history by the adrenals. This has been carried out in the second volume, beginning with page 1389, reserving for the present chapter what disorders could strictly be associated with the adrenals *per se* or due essentially to an excess of adrenal tissue, as in the various forms of hypernephroma.

In point of frequency, subdivision of the subject is not difficult to establish, the first condition, treated below, being one which the general practitioner is liable to meet at any moment and continuously in the course of his everyday work.

ACUTE HYPERADRENIA AND ADRENAL HÆMORRHAGE.

By the term "acute hyperadrenia," I mean excessive functional activity of the adrenals or "hyperadrenalism," brought on by the presence in the blood of the system at large of any poison capable of exciting the adrenal center.

We have seen that various toxics, pneumobacillus cultures, diphtheria and other toxins, drugs, vegetable poisons, etc., caused, when injected experimentally, congestion of the adrenals, so marked in some instances as to provoke rupture of the congested vessels, or necrosis of the adrenal cellular elements compressed by them. To the confirmatory investigations already mentioned may be added those of Bernard and Bigart,[216] who studied the effects of arsenic, mercury, and lead, mainly in respect to the histological changes produced in the cellular elements of the adrenals, and who found that in the *less profound* intoxications there occur, instead of destructive lesions, the histological signs of *functional hyperactivity*. My own investigations have not only sustained this conclusion, but they have served to explain the manner in which this functional hyperactivity is brought about, viz., by excitation of the adrenal center, which, as already stated, I traced to the pituitary body.

As previously shown, we are dealing with the manifestation of an immunizing function in which the adrenals take part. Important to recall in the present connection, however, is that, when the intoxication becomes excessive, it may entail grave consequences. The intra-adrenal vascular channels, abnormally engorged through the marked back pressure induced by the high blood-pressure caused by the excess of adrenal secretion, are exposed to rupture. This hyperactivity of the adrenals (acting in conjunction with the thyroid) constitutes the phenomenon, so far unexplained by pathologists, of *fever*, while the excessive activity which exposes the adrenal vessels to rupture coincides with that of *hyperpyrexia* in these acute infections. In other words, the hyperadrenia which occurs in the course of acute febrile infections or intoxications is the expression of an immunizing process, but this assumes dangerous proportions and involves the danger of fatal adrenal hæmorrhage when excessive, *i.e.*, when the immunizing process exceeds certain limits.

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[216] Bernard and Bigart: Jour. de physiol. et de pathol. générales, No. 6, p. 1014, 1902.

Acute hyperadrenia, therefore, *is that condition of the adrenals which precedes adrenal hæmorrhage in any febrile infection or intoxication, and the danger-signal of which is hyperpyrexia.*

This does not mean that febrile infections and intoxications alone expose the adrenals to hæmorrhage; we have seen that many poisons and drugs even may do so by raising or depressing unduly the blood-pressure through a direct action on the vasomotor center. This process has been reviewed in sufficient detail. We shall now deal only with diseases due to toxins and endogenous poisons, toxic wastes, etc., that are capable of enhancing the adrenal functions to awaken a defensive process and, as a complication, adrenal hæmorrhage, and treat both conditions jointly, the better to emphasize their close clinical relationship.

Adrenal hæmorrhage first described as a disease by Rayer[217] early last century, and cases of which have been reported by Addison, is of common occurrence pathologically. Besides the evidence previously submitted illustrating the frequency with which this morbid process is observed may be mentioned the fact that, in 150 random autopsies, Loeper and Oppenheim[218] found, aside from instances of simple congestion, which were very numerous, 5 true hæmorrhages visible to the naked eye and 8 discernible microscopically. The proportion was much greater when infectious diseases had been the cause of death; and they hold that a large number of similar lesions are masked by cadaveric changes: adrenal congestion and necrosis being frequently present together. The newborn showed a special predisposition to this complication, the proportion of 250 autopsies being 45 per cent. That we are dealing with a frequent, though generally overlooked, cause of death, is evident.

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[217] Rayer: L'Expérience, May 10 and Nov. 10, 1837.
[218] Loeper and Oppenheim: *Loc. cit.*, p. 732.

While disorders of respiration predominate as cause in the newborn, infections do so in children and adolescents. Then come, in order, and, apparently, as the most frequent causes in adults: pulmonary disorders, especially tuberculosis and pneumonia; nervous diseases, particularly meningitis and epilepsy; chronic renal diseases, arteriosclerosis, cancer, abscess, burns, and general paralysis of the insane. Purpura is often regarded as a cause, but this should be considered, from my viewpoint, as a precursor or danger-signal of adrenal hæmorrhage, though the purpuric spots, which are in reality cutaneous hæmorrhages, persist after the adrenal hæmorrhage has occurred.

From the facts submitted below, I would define adrenal hæmorrhage as *an extravasation of blood into one or both adrenals due to rupture of some of their blood-vessels when, as a result of high blood-pressure throughout the body from any cause: toxins, toxic wastes, etc., these vessels are subjected to centrifugal pressure exceeding the resistance of their walls.*

PATHOGENESIS AND SYMPTOMATOLOGY.—Although adrenal hæmorrhage is due to the rupture of the vascular elements when the congestion of hyperadrenia exceeds safe limits in all cases, the pathogenesis of adrenal hæmorrhage varies considerably in its general lines according to the age at which it occurs. This applies also, to a limited extent, to the symptomatology. It becomes necessary therefore to divide the cases into three general groups, viz.: (1) the newborn, *i.e.*, during the first days of life; (2) children, up to puberty, and (3) adults, *i.e.*, beyond puberty.

Adrenal Hæmorrhage in the Newborn.—In these, adrenal hæmorrhage occurs within a few moments or days after birth. In a small proportion of cases, death ensues, without premonitory symptoms, shortly after birth. Delay or injuries in the course of delivery or interference therewith by malpositions, or any of the causes which are apt to render artificial respiration necessary, predispose to it. In another class of cases the infant, having shown perhaps some slight difficulty in breathing or a tendency toward cyanosis, suddenly ceases to nurse; reddish-purple or bright-red spots of purpura appear on the face, neck, buttocks, or extremities; a convulsion follows, with death in its wake. Or again, patches of purpura appear, the infant refuses the breast and becomes somnolent, then suffers from colic, diarrhœa, vomiting, and fever and becomes rapidly emaciated. Convulsions usually precede death.

All such cases are due, from my viewpoint, to the inadequacy of the defensive resources of the infant, *i.e.*, its inability to counteract an endogenous toxæmia. As previously stated and as will be emphasized later, the adrenal system (consisting of the adrenals, thyroid, and pituitary, and to which I attribute a leading rôle in all immunizing functions) is not sufficiently developed in the nursling to protect it adequately against toxics of various kinds; the maternal milk provides the immunizing constituents derived from her own adrenals and thyroid to compensate for this function. My opinion was experimentally sustained by Fassin, Stepanoff, and Marbé,[219] and also by Concetti[220] as to the influence of the thyroid in the process, while the immunizing property of maternal milk as a compensating factor for the deficiency of the suckling has been sustained by Ehrlich and Brieger, Abraham Jacobi, Welch, and others. Now, at birth, any condition which diminishes materially the immunizing activity of the maternal milk, or which, in the nursling, interferes with the utilization of the maternal immunizing bodies, such as a deficient intake of oxygen, asphyxia, hypocatabolism, etc., correspondingly impairs the power of the infant to break down its waste products, thus allowing these poisons to accumulate in the blood. Precisely as they are known to do in epilepsy, eclampsia, and other convulsive disorders, these endogenous intermediate wastes cause a violent elevation of the blood-pressure,—sufficient to cause rupture of the delicate but rich vascular network of the adrenal medulla, localized capillary hæmorrhages in the skin, *i.e.*, the purpura, melæna, hæmoptysis, epistaxis, and other forms of hæmorrhage witnessed. Vomiting and diarrhœa occur as results of the marked congestion in the alimentary canal, while convulsions are produced by a corresponding hyperæmia of the cerebrospinal axis.

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[219] Léopold Lévi and de Rothschild: Physio-pathologie du corps thyroïde, p. 29, Paris, 1911.

[220] Concetti: Revue d'hygiène et médecine infantiles, Nó. 2, 1910.

This accounts for the fact that these cases cannot be traced to infection or ascribed to the presence of any pathogenic organism (though we shall see presently that infection often causes adrenal hæmorrhage in older children), and also for the frequency of adrenal hæmorrhage the first few days after birth, especially where there is any indication of deficient respiration, or, as in the cases witnessed by Northrup, an incomplete septum lucidum.

The cortex is sometimes greatly distended by the hæmorrhage, and the friable medulla of the organ completely disorganized and replaced by a black blood-clot.

Adrenal Hæmorrhage in Children.—This is due to an entirely different class of causes, though the morbid effects and the symptomatology are very similar. Here again death occurs sometimes more or less suddenly in the course of the causative disorder, or, in fact, sometimes before its exact nature has been determined, though in most cases the lethal collapse is preceded by purpuric spots. If the causative disorder be an exanthema, varicella, for example, the eruption may itself show a change, each patch assuming a bluish or cyanotic tinge, soon followed by collapse. In most cases, however, there occurs two, three, or more of the following symptoms: vomiting, fever, marked prostration, a more or less extensive petechia or a purplish purpuric eruption, dyspnœa or at least rapid respiration, diarrhœa with perhaps abdominal pain radiating into the loins, due to pressure of the dilated adrenals upon the adjoining sympathetic plexuses, and convulsions, cyanosis, and collapse—forming an incomplete and variable syndrome which is characterized by a feature common to all—its rapid termination in death, *i.e.*, within a period varying from a few to forty-eight hours.

That a toxæmia underlies all cases, as in the newborn, is also evident: but its source is entirely different. Adrenal apoplexy has been met in the course of several of the exanthemata, varicella, variola in the unvaccinated, diphtheria, and scarlatina especially; during convulsions or as a complication of abscesses, pyæmia, septicæmia, hydatid cysts, bronchopneumonia, ptomaine poisoning, or after extensive burns and severe injuries.

It has also been attributed to the staphylococcus pyogenes aureus and albus (Riesman, Dudgeon), the streptococcus (Drysdale), the pneumococcus and bacillus coli communis (Rivière), the meningococcus (Candler), and to other micro-organisms. On the whole, it may be due to many morbid conditions; but the one striking feature of all these causative disorders is that they are all of such a nature (febrile diseases, convulsions, etc.) as to provoke a rise of blood-pressure. Just as we have seen the latter to be the cause of adrenal hæmorrhage in the newborn, so is it in children. Dudgeon[221] states that "any disease which is known to produce stagnation of the blood in the veins or a marked increase of the blood-pressure may be associated with adrenal hæmorrhage"; I would say instead that such a condition of the circulation tends to *produce* the latter as a complication.

Here again we are likely to find one or both glands more or less filled with a black coagulum with, occasionally, extravasation, or here and there hæmorrhages into the medulla or under the cortex, raising the corresponding portion of the latter.

Adrenal Hæmorrhage in Adults.—Adrenal hæmorrhage in adults is now thought to be rare, but this is probably due to the fact that it is seldom recognized. Although sudden death may occur without premonitory symptoms of the hæmorrhage in the adrenals, there is usually more or less sudden pain—sometimes excruciating—in the abdomen, radiating toward the back, under the costal margin; tympanites, vomiting, prostration, great weakness, copious and stubborn diarrhœa. Hæmorrhagic purpura and cutaneous hæmorrhages may also appear, but purpura is much less common than in children; anæmia, with a yellowish tinge of the skin ranging from sepia or light brown to the bronzing of Addison's disease in which adrenal apoplexy is not uncommonly observed. When it occurs in the midst of a convulsion, during an epileptic fit, for example, the patient may either die on the spot or show, on recovery, unusual asthenia, with, perhaps, uncontrollable diarrhœa. Gradually the pulse and respiration become weak, more or less cyanosis appears, followed by coma and death. Unusual physical exertion has also been known to cause adrenal apoplexy and sudden death. Acute nephritis is an occasional cause, death occurring suddenly with, perhaps, symptoms of pulmonary œdema.

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[221] Dudgeon: Amer. Jour. Med. Sci., Jan., 1904.

The prevailing feature of adrenal hæmorrhage in adults is the presence of lesions in the adrenals themselves which cause these organs to yield with abnormal facility when a general rise of blood-pressure is brought on by any one of many causes. In adrenal apoplexy occurring in the course of Addison's disease, for example, the tissue-wastes which accumulate in the blood as a result of the diminished antitoxic power of the diseased adrenals excite, we have seen, the vasomotor center, and increase in proportion the vascular tension and blood-pressure. In the course of an epileptic fit the same exciting cause prevails, since, as is well known, the vascular tension is always marked. Over-exertion may produce adrenal hæmorrhage through the same mechanism, owing to the accumulation in the blood of an excess of tissue-wastes. Acute nephritis also produces it by raising the vascular tension; in a case of this kind reported by Loederich[323] this feature of the case is specifically noted. The production of adrenal apoplexy in Addison's disease by injections of adrenalin has also been reported in 2 cases (Boinet) —owing obviously to the rise of blood-pressure which this agent produces. Common to adults also is the form due to arterio-sclerosis, the adrenal intrinsic arteries yielding here, as they do in the brain, owing to atheromatous degeneration, when from any cause the blood-pressure exceeds certain limits.

On the whole, it is apparent that adrenal hæmorrhage presents many features in common with cerebral hæmorrhage in which the gradually weakened vessel, particularly where, in the case of adults, arteriosclerosis prevails, can no longer sustain anything beyond the minimum blood-pressure.

Many auxiliary factors tend greatly, however, to impair the resistance of the adrenal vessels and tissues. As shown by Claude Bernard, hyperæmia is a cardinal feature of function. The adrenal vessels are already congested and under stress, therefore, when they are submitted to the excessive centrifugal tension which a marked rise of blood-pressure entails. Again, in the light of modern researches, and as will be demonstrated later in this work, the blood contains, during the febrile stage of infections and intoxications, bactericidal and antitoxic bodies to which autolysis, under certain conditions, is ascribed. That the rich vascular elements of the adrenals and even the delicate adrenal medulla are probably subjected to such a process and thus rendered more vulnerable, in the course of acute febrile infections, is suggested by the areas of necrosis in these structures which many autopsies reveal. I must state, however, that I am not inclined to accept the conclusion that these necrotic areas are due to post-mortem changes, and that I regard them as due more to a process of autodigestion similar to that known to exist in the gastric mucosa. This subject cannot, however, be considered here.

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[323] Loederich: Le Bulletin Médical, July 8, 1903.

DIAGNOSIS.—The most important feature in this connection is to differentiate clearly the prehæmorrhagic from the posthæmorrhagic phenomena. Careful attention in this particular makes it possible to save life, since the prehæmorrhagic symptoms include several which may be regarded as danger-signals to the effect that the blood-pressure is dangerously high, and that the adrenals are threatened.

In the *infant,* imperfect respiration following delayed delivery, purpura with or without fever points clearly to impending hæmorrhage: The course of events then, if no prophylactic measures are taken, will be the appearance in a few hours of the posthæmorrhagic state: abdominal pain, diarrhœa, vomiting, soon followed by a gradual decline of the temperature, coldness of the extremities with convulsions or cardiac collapse as terminal phenomena.

In the *child,* the presence of fever and high blood-pressure in the course of any infection entail the possibility of adrenal hæmorrhage, especially when any eruption that may be present tends to spread, or where purpuric spots are present. Here again, if not avoided by appropriate treatment, the posthæmorrhagic phenomena appear, likewise ending in death in a few hours.

In the *adult,* the great variety of disorders which, besides the acute infections, adrenal hæmorrhage may suddenly complicate would seem to preclude the possibility of preventive measures, but if it is remembered that the adrenals are exposed to hæmorrhage *whenever the blood-pressure is high from any cause,* as suggested by venous engorgement, venous pulse, facial congestion, and a hard pulse, with the sphygmomanometer as control, the danger can as readily be forestalled as in the young. We must also, in the adult, take into account the possibility of adrenal hæmorrhage in all asthenic diseases of the adrenals themselves, particularly the tubercular lesions of Addison's disease in which death frequently occurs suddenly. In all of these, the symptoms of hypoadrenia are present, particularly muscular asthenia, emaciation, hypothermia, hypotonia or low blood-pressure, and feeble pulse.

The onset of adrenal hæmorrhage in adults is characteristic in its abruptness, the severity of the abdominal pain, and the rapidity with which it is followed by general collapse. The incoercible vomiting and diarrhœa (either one or both), the hypothermia, the cold sweats, the feeble pulse and heart action, the coma or convulsions with sudden death in their trail are unmistakable signs of sudden arrest of the adrenal functions.

The absence of all reference to adrenal hæmorrhage in text-books has caused it to be mistaken for arsenic poisoning and other intoxications, cholera morbus, appendicitis, cerebral apoplexy, and other acute disorders.

PROGNOSIS.—As will be shown presently, adrenal hæmorrhage may be followed by the development of hæmatomata in the adrenals proper, proof evident that not all cases are necessarily fatal, particularly small hæmorrhages located in the depths of the organ. It is probable, therefore, that when the likelihood of this complication will be borne in mind by the practitioner when treating any one of its many causes, and its main cause, excessive vascular tension, generally recognized and counteracted, its present high mortality will be greatly reduced.

TREATMENT.—The multiplicity of pathogenic factors and of symptoms, sufficient to have suggested many clinical types to various authors, has, so far, prevented the elaboration of any treatment calculated to prevent or arrest adrenal hæmorrhage and its rapidly fatal course. With excessive blood-pressure as the direct cause of the disruptive congestion of the adrenal vessels, however, a general line of treatment calculated to relieve it obviously imposes itself.

In a threatened case, antipyrin or other coal-tar products suggest themselves; but their use cannot but prove pernicious, owing to the primary action on the vasomotor center. By exciting this center and raising the blood-pressure they increase the likelihood of adrenal hæmorrhage, a fact which probably accounts for the many instances of fatal collapse observed under their use in acute febrile diseases. The physiological saline solution offers, on the other hand, all desirable qualities. It does not, as argued theoretically by some authors, increase the vascular tension, even if injected intravenously; as shown by the experiments of Sollmann,[223] Briggs,[224] and others, any excess of fluid leaves the vessels at once. By reducing the viscidity of the blood, saline solution tends to relax the blood-vessels; by increasing its osmotic properties, it facilitates greatly the penetration of the plasma into the lymphatic channels, thus further reducing the vascular tension. The bactericidal and antitoxic properties of the blood are not reduced in the least by this procedure; there is considerable evidence available to show, in fact, that they are enhanced (see p. 1367). Saline solution, therefore, should be used intravenously in emergency cases; subcutaneously in threatening cases, and per rectum in all cases in which there is any likelihood whatever that adrenal hæmorrhage might occur. If employed from the onset of all infections, as I suggested in 1903, the blood-pressure would probably never be raised sufficiently to endanger the adrenals.

As to drugs, we have several at our disposal which lower the blood-pressure. In emergency cases, nitrite of amyl by inhalation, with nitroglycerin (or in children the sweet spirit of niter) to sustain the effect, appears indicated. Chloral hydrate has been used advantageously by J. C. Wilson in certain exanthemata, to subdue the cutaneous discomfort and as a sedative; as it is also a vasomotor depressor, it might also serve advantageously in all but infants in whom the respiratory mechanism is defective. Veratrum viride suggests itself as another useful agent of this class. Of all measures, however, the saline solution is much to be preferred.

When the hæmorrhage has occurred, the lethal phenomena are of such short duration in most cases as to have suggested, we have seen, the term "adrenal apoplexy." In a fair proportion of cases, however, the hæmorrhage causes sudden hypoadrenia. The treatment of this condition is that indicated in the emergency cases of terminal hypoadrenia (see page 113). If the hæmorrhage has not been too extensive the chances of recovery will be greatly increased by the use of adrenal or pituitary preparations, the latter owing its properties, in my opinion, to the adrenal chromaffin substance the pituitary contains.

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[223] Sollmann: Archiv f. exp. Path. u. Pharm., Bd. xlvi, S. 1, 1901.
[224] Briggs: Johns Hopkins Hosp. Bull., Feb., 1903.

ADRENAL HÆMATOMA.

(*Adrenal Hæmorrhagic Pseudocyst.*)

Adrenal hæmatoma, which usually develops in but one adrenal, occurs as a complication of the condition just reviewed. It becomes a source of fatal adrenal hæmorrhage when the cyst breaks and empties its contents into the abdominal cavity. It indicates that the form previously described is not always fatal, but also that the lesions left behind may serve as the initial lesion of another grave disorder. Especially does this apply when but one adrenal is the seat of hæmorrhage. Its original causes, when these are traceable, are the same as those of the acute form: acute intoxications, especially diphtheria, typhoid fever, burns, osteomyelitis, hepatic abscess and tuberculosis, atheroma of the adrenal arteries, thrombosis of the adrenal veins, traumatisms, etc.

Pathogenesis and Symptomatology.—While older investigators, including Klebs, Virchow, and Heuschen, considered these growths as retention cysts similar to those formed in the thyroid, and thus termed them "struma adrenalis," the prevailing view at the present time is that a small hæmatoma or an acute congestive process initiates the growth. As the latter increases in size, the adrenal structure is gradually destroyed and the contents is no longer—unless a recent hæmorrhage has occurred—merely blood, but a more or less fluid magma of detritus, broken-down blood- and tissue- cells, flakes of fibrin, cholesterin crystals, etc., which may be dirty yellow, greenish, or brownish in color. Microscopically the walls of the cyst, which vary from 1/16 to 1/8 inch in thickness, are composed of fibrous tissue; the inner aspect shows shreds or remnants of the adrenal cortex. Certain thickened portions of the capsule and what semiorganized clots the cyst may contain may be found to contain small cysts and chalky deposits. These growths sometimes become very large—as large as an adult head in a case of Chiari's—and contain several pints of blood or liquefied blood and tissue elements.

The symptomatology of adrenal hæmatoma introduces but little, if anything, of the symptom-complex of adrenal insufficiency (hypoadrenia) or overactivity (hyperadrenia), since the functions of the organs are not affected materially—otherwise than by pressure in some instances—owing to the ample margin (eleven times the actual needs of adrenal tissue) left undisturbed. Adrenal hæmatoma may, in fact, give rise to no symptom other perhaps than a sensation of weight, until quite large, when pain supervenes. This is at first indefinite, though most marked in the region of the tumor, in the right or left loin, or in the upper portion of the abdomen and loin. The neuralgia-like pain due to pressure upon the adjoining sympathetic plexuses becomes increasingly severe, and radiates in various directions, especially toward the hip and thigh of the corresponding side, and is subject to exacerbations, which may be very severe, especially after meals. Epigastric pain and vomiting (the latter of which affords relief) occur in some cases, especially during these exacerbations of suffering.

The tumor may manifest itself, at first, merely by enlargement of the abdomen. The bulging then becomes more clearly defined on one side or the other (this variety of growth being almost invariably unilateral) under the lower ribs, which may be pushed outward if the growth is sufficiently large, or below their free border, *i.e.*, between them and the superior spine of the ilium. If the tumor, which grows downward and forward, is sufficiently below the ribs to be palpated, it is usually found globular, or oval, smooth and tense, though elastic, to the touch. Fluctuation may also be elicited. In some cases it is immovable under palpation, though it may, at first, follow the respiratory movements. Nor can it be grasped as is sometimes possible in renal tumors; if small the tumor is movable either upward or downward, but this mobility gradually decreases as the tumor develops. The growth is sometimes sensitive under pressure.

At first, several years perhaps, the patient may appear normal in every other respect, be well nourished, ruddy, etc. With comparative suddenness, however, he begins to fail, losing flesh rapidly, all the other symptoms mentioned, to which dyspnœa and a sense of constriction about the chest is added, becoming more severe. If the cyst does not rupture, polyuria, hæmatùria, and even slight bronzing may appear. It is probable, however, that this train of phenomena is witnessed only in a very small proportion of cases, rupture and hæmorrhage, constituting the "adrenal hæmorrhage" in adults treated under the preceding heading, being the outcome in practically every instance. Here, however, the rupture is external, giving rise to peritoneal manifestations—if these have sufficient time to develop at all.

Diagnosis.—The symptomatology of adrenal cyst apart from the location of the tumor does not present, as just shown, very characteristic features. The location of the pain sometimes suggests intercostal neuralgia; but, inasmuch as pain occurs only when the growth is large, percussion and palpation will reveal the presence of a tumor. In neuralgia the pain is also apt to be localized, thus distinguishing it from the radiating pain of adrenal cyst. The sudden onset of severe pain may be taken for acute pancreatitis. The location of pain and tenderness in the upper left abdominal quadrant, the subnormal temperature, and the early lethal trend—death occurring sometimes within three days—clearly point to the latter disease. Pancreatic cyst is also differentiated by its location and its association with glycosuria, stearrhœa, and imperfect digestion of fats and albuminoids. Hydatid cyst of the liver, another source of confusion, is attended by the presence of biliary pigments in the urine, the appearance of cysts in the stools and vomited matter, and with obstruction phenomena. Cancer of the spleen may be recognized by the more nodular outline of the growth and the cachectic phenomena. Hydatid cyst of the spleen is usually associated with hydatid cysts elsewhere and may be accompanied by the presence of hooklets in the excretions. Puncture of the growth should be carefully avoided when there is any suspicion whatever that an adrenal blood-cyst is present. Renal cysts are more easily palpated bimanually, and are usually freely movable.

The sudden appearance of symptoms of severe internal hæmorrhage (the adrenal hæmorrhagic cyst having ruptured into the peritoneal cavity or the subperitoneal cellular tissue), *i.e.*, the acute abdominal pain and other phenomena of collapse, etc., of adrenal hæmorrhage with death within a few hours or days, may first reveal the existence of adrenal hæmatoma; but in most cases it develops sufficiently to produce the pressure symptoms just described.

PROGNOSIS.—The fact that adrenal hæmorrhage is practically always unilateral, and that the loss of one adrenal does not compromise life, as does removal of both organs, makes it possible to remove the growth with safety. The frequent instances of severe collapse and shock that have followed these operations suggest that the operative prognosis cannot but be improved by resorting to those surgical procedures which will entail the least possible handling of the intraperitoneal organs and of the sympathetic ganglia, all of which are well known to produce shock readily by reflex action.

TREATMENT.—The cyst may be removed through either an abdominal or lumbar incision. In accord with M'Cosh's advice, which a review of the operative results recorded fully sustains, preference should be given to the lumbar incision. The approach is more direct; it avoids the handling of the intraperitoneal organs, which must necessarily take place if the tumor be reached through the abdominal incision, and it affords the most direct route for drainage. In the average case, an oblique incision from behind downward and forward below the last rib, which has been found most convenient for extirpation of the kidney and ureter, is as applicable here. If much space is needed it is safer to remove the last rib than, as some European surgeons have advised, to resort to the abdominal incision, which, as previously stated, entails considerable shock. The tumor is sometimes found so firmly adherent to the kidney that removal of this organ becomes necessary.

HYPERNEPHROMA.

This name has been given to tumors formerly considered as lipomata, adenomata, or myxomata, but shown by Grawitz, in 1883, to be developed from adrenal tissue, either within the adrenals themselves or in the kidneys, the walls of blood-vessels, or other structures in which "adrenal rests" (fragments of misplaced adrenal tissue) or "aberrant adrenals" occur.

From my viewpoint, these so-called "adrenal rests"—found in 90 per cent. of all autopsies by Bayard Holmes, at least once a week by Grawitz in his autopsies, etc.—are not misplaced fragments of adrenal tissue; they belong normally to the kidney and many other organs, even though composed usually of cortical adrenal tissue. I have submitted the view[225] that what has been termed the internal secretion of the kidney is a product which differs in no way from that of the adrenals, and[226] that the kidney and the adrenals were governed by the same nervous structures, being thus closely linked functionally. Under the influence of centric impulses the so-called adrenal rests and the adrenals are both caused to increase their secretory activity and to enhance the intrinsic metabolism of the tissues they supply. In some instances "adrenal rests" are composed of both cortical substance and chromaffin substance found in all sympathetic structures by Kohn, Wiesel,[227] and others.

Hypernephromas are relatively common in the kidney, constituting, as shown by Albarran and Joubert, 17 per cent. of all renal tumors; they are much less frequently found in the adrenals proper or in other organs, such as the uterus, ovary, the broad ligament, etc. Microscopically, they present the typical characters of the adrenal cortex and closely, as a rule, invest vascular channels. These vessels and adjacent tissues usually contain a colloid material similar to that found in the thyroid, or secreted by the adrenals. They are benign at first and become troublesome—sometimes after many years—mainly on account of their size, which sometimes reaches that of a child's head, but the pressure they exert on surrounding structures, their tendency, even when benign, to metastasize in the lungs, bones, brain, give them their malignancy.

PATHOGENESIS AND SYMPTOMATOLOGY.—Before the local symptoms of the tumor appear—when any are clearly discernible—hypernephroma evokes phenomena which are diametrically opposed to those of Addison's disease, and which correspond with increased nutrition and stimulation of growth such as that produced by thyroid preparations in cretinism.

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[225] Sajous: Monthly Cyclopædia, June and July, 1909.

[226] See p. 467, this volume.

[227] Wiesel: International Clinics, vol. ii. 15th series, 1905.

The symptomatology varies considerably in different cases and suggests that several types exist which our present knowledge does not enable us to discriminate. Some of these exhibit such malignancy that they have been grouped in a separate class. Beginning with hypernephromas of the adrenals proper, we may have:—

Malignant Hypernephroma of the Adrenals.—This growth occurs as a rule between the first and eighth year, especially in girls of the latter age, and causes premature development, so marked in some instances that the child appears, as to size and development, twice or three times its true age. Owen Richards[229] reported a case in a girl of 7 years, who was as tall as a person at 20. The face, genitalia and pubis, and sometimes the whole body are covered with an abundant growth of hair, the external genitalia being as fully developed as in the adult. The body is obese, the appetite and thirst excessive although gastric disorders, including stubborn vomiting, are common. The skin may be swarthy or dark-hued as in a brunette, or coppery. The voice is sometimes harsh and deep. Such children are usually cross and sullen, unlike obese children in whom the obesity is due to deficient fat catabolism. These primary growths of the adrenals, which are usually observed in girls, are of slow development, and years usually elapse before metastasis and pressure phenomena—those which give the growth its malignancy—appear.

The abnormal growth of the child may suggest gigantism or acromegaly due to some disorder of the pituitary body, but the characteristic growth of the extremities, the absence of obesity in these disorders do not occur in hypernephroma.

To explain the abnormal growth, we need not go beyond my own view that the adrenal secretion underlying general oxidation, metabolism and nutrition, excessive functional activity of the adrenals engenders excessive nutrition and overgrowth. But how account for the malignancy of this form of growth? To answer this would bring us within the domain of pure speculation. It is preferable to limit ourselves to clinical facts, pending future developments.

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[229] Richards: Guy's Hospital Reports, vol. lix, pp. 267-282.

Infants and young children are also subject to a form of primary malignant tumor of the adrenals, described by Hutchison, in which, even before the neoplasm, which grows with great rapidity, can be felt in the renal region, there appears a spontaneous—sometimes traumatic—ecchymosis of one or both eyelids, soon followed by (usually unilateral) exophthalmos and metastasis in the skull, and often in other bones, especially the ribs. The preauricular lymph-nodes and those behind the angle of the jaw are enlarged, and the whole temporal region eventually becomes the seat of a malignant growth. Pain in this location and optic neuritis with amblyopia may complicate the case. Death occurs early from anæmia and cachexia. Of the 14 examples reported, 13 were due to sarcoma or lymphosarcoma of the adrenals.

DIAGNOSIS.—Tumor of the orbit in infants and young children should, as emphasized by Tileston and Wolbach,[229] arouse the suspicion of metastases from an adrenal growth. If an abdominal tumor be found it is almost certainly of adrenal origin, and this would be still further corroborated by enlargement of the preauricular glands, which renders the diagnosis of sarcoma of the orbit unlikely. Chloroma presents almost identical growths, being associated with tumors of the orbit in two-thirds of the cases, with exophthalmos usually as the first symptom, but this may be excluded in the absence of leukæmic changes in the blood. Myeloma may cause bony growths about the skull, but is exceedingly rare in childhood; the presence of the Bence-Jones body in the urine would render the diagnosis of myeloma certain, while its absence is not conclusive. Abdominal tumor associated with precocious maturity is practically certain to be of adrenal origin, if tumors of the ovaries or a retained testis can be excluded. Garrow and Kennan[229a] observed a case in which there was a solitary metastasis in the spinal cord.

Hypernephroma of the Kidney.—It is to renal growths developed from the so-called "adrenal rests" in the kidney, that Grawitz, in 1883, gave the name "hypernephroma." They occur more frequently in the kidneys than elsewhere in the body, and constitute a large proportion of all renal tumors, *i.e.*, 17 per cent.

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[229] Tileston and Wolbach: Amer. Jour. Med. Sci., June, 1908.

[229a] Garrow and Kennan: Med. Record, Jan. 17, 1912.

Hæmaturia is often the first and the most frequently observed symptom of renal hypernephroma, having been noted in 90 per cent. of all cases. The hæmorrhages are usually severe and occur intermittently, weeks and even months elapsing between them. Worm-like clots—thus shaped during their passage through the ureters—are often passed. During the intervals the urine is either clear or it may contain red corpuscles. The hæmaturia is increased by exercise and by manipulation of the region overlying the growths if the latter is sufficiently large to be felt. It may be the only symptom of the growth or precede the detection of the latter by palpation as much as ten years. As a rule, however, the tumor (which occurs in 80 per cent. of all cases) is sufficiently large to be detected much earlier, and sometimes immediately after an attack of hæmaturia. It is located in the loin, often on the right side and two or three finger-breadths below the costal margin. It is at first small—about half the size of a walnut—and is movable in about one-half of the cases. As a rule, palpation causes no pain at first, though it may prove tender when directly pressed upon.

Dull pain in the lumbar region suggesting lumbago may be the initial symptom. This pain gradually increases and, after being centered in the region of the growth, with a sensation of weight, increasingly radiates in various directions, the back, the abdomen, and the testicles. It may come on suddenly and last three or four hours, then be followed by hæmaturia and frequent urination followed by a period of rest during which the urine is slightly albuminous. The urine sometimes contains a few casts, oxalate of lime, and a few corpuscles. During this period of rest a certain stiffness may be experienced on the side of the tumor. Varicocele is frequently observed in these cases, on the same side as the focus of pain; it may develop simultaneous with the latter and disappear when the patient assumes the recumbent position.

While periodical hæmaturia, a tumor and pain in the locations mentioned are typical signs of renal hypernephroma, other phenomena may appear gradually as the morbid process advances. Most important among these are the metastases, which occasionally occur as first signs of the disease. This is especially the case in bone metastasis, which may appear in the vertebræ, the ribs and other long bones, the skull, scapula, etc., *i.e.*, practically any portion of the skeleton. Metastasis may also occur in various viscera, particularly the lungs, the consolidation in the latter suggesting the corresponding stage of phthisis.

The arteries may be thickened and show clearly defined signs of arteriosclerosis, quite in contrast sometimes with the relative youth of the patient, and the blood-pressure be quite high. The skin is not bronzed in these cases, but yellowish and, sometimes, swarthy or smoky, this being replaced by pallor when the end is near. The temperature may be raised, but this rarely exceeds 1° or 2° F.

An important feature in this connection is that bronzing is a characteristic of *insufficiency* of the adrenals, as in Addison's disease, whether due to degeneration, tuberculosis or malignant tumor of these organs or of their nerve supply. In hypernephroma, on the contrary, we have an addition of adrenal substance to the circulation through the secretory activity of the adrenal rests, as shown by the familiar results of adrenal overactivity enumerated—high blood-pressure and arteriosclerosis. The icterus or swarthiness here is due, from my viewpoint, to the continuously high blood-pressure which causes the cutaneous capillaries to become hyperæmic and to expose an increased quantity of the adrenal principle—the component of melanin (we have seen in the early portion of this chapter that melanin is the adrenal principle) to oxidation. The stage of bronzing is not reached, because the pigment is not deposited in the cutaneous tissues, as it is in Addison's disease, but merely supplied to them in excess.

The duration of the disease varies from fifteen weeks to eight years. The patient gradually loses flesh and grows weaker, all the symptoms become aggravated, hæmaturia becoming prominent and causing marked secondary anæmia; moderate œdema of the lower limbs may appear mainly as a result of pressure on some large venous trunk, and delirium sometimes precedes the terminal coma.

Diagnosis.—The pain in the region of the affected kidney, the hæmaturia accompanied by frequent urination, and the localized tumor are the chief diagnostic points among those previously enumerated, but other features may serve to facilitate the diagnosis. Gellé pointed out that fragments of the tumor, which is very friable and often dissociated during hæmorrhages, could be found in the clots passed with the urine. The cells preserve their characters and staining properties. As to diagnosis of the tumor itself after removal, Croftan found (1) that a watery extract of fresh hypernephroma, in keeping with adrenalin and adrenal extracts, provoked glycosuria when injected in the rabbit; (2) that a pure starch solution to which the watery extract of hypernephroma was added contained an appreciable quantity of dextrose, and (3) that the watery extract also possesses the power to decolorize an iodine starch solution. These simple tests make it possible to differentiate hypernephromata from other tumors of the kidney. This is important, since the post-operative prognosis of hypernephroma is much more favorable than that of any other malignant tumor of the kidney. A high blood-pressure tends greatly to insure the diagnosis.

Various disorders may be simulated by hypernephroma, prominent among which is urinary calculus. In this connection the pain is coincident with the hæmorrhage, while in hypernephroma the pain continues after the latter, though greatly relieved. The vermicular and cylindrical shape of the clots in hypernephroma is also suggestive. Cystoscopic examination at this time often reveals these clots projecting from the ureter of the diseased kidney, whose tumor can also, in some instances, be discerned under X-ray examination. Pregnancy is sometimes suggested when the growth projects anteriorly, especially in view of the fact that amenorrhœa sometimes precedes the abdominal enlargement.

Hypernephroma may be mistaken for enlarged spleen. The latter is usually nearer the surface and its mobility on inspiration more marked. It is located on the left side, whereas hypernephroma, in most instances, occurs on the right side. Catheterization of the ureters may serve to indicate, between the periods of hæmaturia, which of the two kidneys is most impaired functionally. The blood count affords little if any information, any diminution of red corpuscles—sometimes to an extreme degree—being readily accounted for by hæmaturia.

Moderate leucocytosis occurs in some cases, but not with sufficient frequency to give this sign any diagnostic importance.

In some cases the symptoms and physical signs other than hæmaturia afford but little help to establish the identity of the tumor, either anteriorly or posteriorly. In that case, the absence of pregnancy being clearly established, an exploratory incision followed immediately, if hypernephroma be present, by its radical removal, is indicated.

PATHOLOGY.—Hypernephroma is usually located in the upper pole of the kidney, immediately, therefore, under the adrenals. When found early in life at autopsies it may be no larger than a lentil or even smaller, but it may attain the size of a child's head, growing outwardly or, in some cases, inwardly at the expense of the renal tissues. These growths reproduce more or less perfectly the adrenal tissue, the smaller growths being made up, as a rule, of the cortex, and the larger of both the cortical and the medullary substance. They are firm when small, but when they attain a certain size their tendency is to become lobulated, the projecting masses becoming softer and cyst-like. They are lobulated owing to the fibrous bands derived from the renal capsule, and the lobules when opened may be yellowish, grayish red, or brown or blackish, and contain hæmorrhagic areas—the source of the blood which causes hæmaturia.

The larger growths are those which tend to become malignant and to produce metastases. These occur through the blood-vessels, both the arteries and veins; the bones and lungs, as previously stated, are the structures most frequently invaded, though, occasionally, extension occurs by the lymphatics, including the retroperitoneal glands.

Microscopically, they usually show a scanty stroma composed of vascularized connective tissue in columns and a parenchyma formed of endothelial polygonal or columnar, translucent nucleated cells which differ entirely from those of the renal epithelium. The cytoplasm is granular and contains, besides detritus and giant-cells, numerous fat-laden vacuoles. It is the presence of considerable fat thus disposed which first caused these tumors to be regarded as lipomata. The fat contains lecithin. Glycogen is also present; sometimes in relatively large quantities.

Prognosis.—As a rule, hypernephromata grow slowly at first, months and even years elapsing before they metastasize or show other signs of malignancy. They may then progress very rapidly and, the hæmaturia becoming continuous, death occurs from exhaustion.

When the growth is thoroughly removed before this stage of malignancy is reached, it shows no tendency to recur.

Treatment.—An exploratory incision is warranted, as previously stated, when an abnormal growth in the abdomen or in the region of the kidney occurs coincidently with hæmorrhage, even when other symptoms of hypernephroma are not present. The majority of authorities consider this procedure advisable, even when hæmorrhage into the bladder cannot be accounted for. In some cases discomfort or tension over one kidney, and deep comparative palpation on both sides may suggest which side should be explored first, but if this unilateral examination fails to indicate the presence of a growth exploration of the other kidney is justifiable. In some instances, the organ is merely enlarged, especially toward the upper pole, or at the hilum. Removal of the growth may be performed extraperitoneally through a lumbar incision. The fatty capsule should, according to Kuzmik, be removed along with the growth, as it may be infiltrated and thus lead to recurrence.

CANCER OF THE ADRENALS.

Primary malignant tumors of the adrenals are generally regarded as rare, but it is probable that when the symptomatology of these growths will be known by the profession at large instead of, as at present, by very few of its members many deaths now attributed to Addison's disease in adults and to asthenic disorders in children will be found to be due to this class of growths. Addison, in fact, included these neoplasms among the etiological factors of the disease which bears his name, but it is now plain that the two syndromes differ in many respects, and that the treatments indicated—medical in the one, and surgical in the other—impose the need of recognizing malignant neoplasms of the adrenals as distinct morbid entities.

Varieties.—Primary malignant tumors of the adrenals are of the various forms of *sarcoma* those most frequently met with and which occur, in the majority of instances, in infancy, childhood, and adolescence; *carcinoma* which occurs, as a rule, in adults or aged subjects. Among the rarer varieties may be mentioned the *malignant hypernephroma* and a class of tumors termed by Prudden *hæmorrhagic adenoma,* i.e., the growths reviewed under the preceding heading. They appear much earlier in females than in males.

While 24 cases of malignant growths collected by Rolleston and Marks included 15 of sarcoma and 9 of carcinoma, 67 collected by Ramsay included 30 of sarcoma and 37 of carcinoma. This tends to suggest that the two forms occur about evenly.

SYMPTOMS.—As a rule, the general phenomena develop insidiously, the adrenal lesion being well advanced when they begin to appear. The strength wanes more or less rapidly; the weight gradually decreases; the pulse and cardiac action become increasingly weaker and more rapid; the temperature shows exacerbation of a couple of degrees at times, but the advanced cases are usually subnormal; the appetite decreases; digestive disturbances, such as nausea, vomiting, flatulence, and diarrhœa, are commonly observed. Anæmia is sometimes manifest, the hæmoglobin being often reduced to 50 per cent., and the red corpuscles to 3,000,000 or less. Cough, with bronchial râles, localized dullness, and hæmoptysis, are occasional complications, while dyspnœa and increase of the number of respirations are apt to occur in advanced cases. The skin may remain normal, but various degrees of pigmentation, ranging from slight icterus to actual bronzing, are observed in the majority of cases. The typical facies may alone be present in cases of primary carcinoma.

This symptomatology is based on an analysis of 60 reported cases of primary malignant tumors of the adrenals. The phenomena are clearly explained by the functions I attribute to the adrenals. Being the purveyors of the secretion which—as the albuminous constituent of hæmoglobin—sustains oxygenation and metabolism and therefore nutrition, increasing emaciation, weakness, hypothermia, the decrease of hæmoglobin, etc., are but normal results, all the other phenoma being secondary thereto. The cases in which no pigmentation of the skin occurs are usually those in which but one adrenal is involved.

All these phenomena are seldom witnessed in a single case. As a rule, after a period of progressive emaciation and adynamia, a tumor can be detected by palpation posteriorly below the costal margin, close to the vertebral column. The mass at first follows the respiratory movements and recedes under pressure, but it eventually becomes fixed and immovable. In some cases, especially in infants, the tumor cannot be detected in this manner, but the abdomen gradually enlarges with a steady increase of the line of dullness, though perhaps no other symptom be discernible. When the outline of the growth can be clearly followed with the fingers, its border is not nodular as in hepatic cancer, but smooth.

Pain is sometimes complained of; it may be located in the region of the tumor; or, radiating upward or across the back, it may extend to the shoulders. The pain has been attributed to the phrenic nerve, but a clearer explanation is the effect of the traction by the tumor, upon the sympathetic ganglia and through the greater splanchnic, upon the sympathetic chain, which is merged in with the mass of nerves, including the brachial plexus, in the tissues of the shoulders.

Pressure symptoms are apt to complicate a case of long duration. Ascites, general œdema, or œdema of the ankles or legs are commonly observed in such cases, due notably in most instances to pressure upon the inferior vena cava. Gangrene of the feet has also been observed. In carcinoma, metastasis is most common in the liver and lungs; in sarcoma it is not quite as frequent and occurs in most cases in the liver and kidney.

Death may occur suddenly, preceded by very few of the above symptoms, especially the sarcomata of infants. In the majority, however, especially in adults, the morbid symptoms gradually develop and the asthenia increases until unconsciousness, labored breathing, and coma terminate in death.

Infants may also suffer from a congenital type of adrenal tumor which simultaneously invades the liver. It is encountered as a congenital tumor, during the first weeks of life. The abdomen becomes increasingly distended; there is moderate emaciation, but no jaundice, pigmentation, ascites, or even pain, the child nursing almost up to the time of death. William Pepper[339] described a series of 6 cases, including a personal case, showing that congenital sarcoma of the adrenals and liver constitutes a special type of malignant disease with its own peculiar symptoms and pathological findings: Swelling of the abdomen occurred within a period ranging from birth to five weeks, thus indicating the congenital nature. The infants lived from one to sixteen weeks, thus showing great malignancy. The increase of growth could be discerned from day to day, thus illustrating rapid development. All were females. The entire normal liver structure was practically destroyed in all. The suprarenal growth exhibited the peculiarity of being very hæmorrhagic. No other part of the body was involved by the new growth.

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[339] Pepper: Amer. Jour. Med. Sci., Mar., 1901.

DIAGNOSIS.—The diagnosis of malignant tumor is not difficult when the tumor is sufficiently large to be discovered by palpation, especially when paræsthesia over the kidneys. This and the asthenic phenomena point clearly to the adrenals, especially if jaundice or any pigmentation of the skin be present. Unfortunately the morbid process is far advanced as a rule when these signs appear. The tumor has been mistaken for psoitis and abscess and phrenic abscess. From hepatic cancer it differs in that the surface of the tumor is smooth instead of lobulated. Of course the possibility of metastasis in the liver, its most frequent seat, must be borne in mind. Hydatid cyst may be suggested, but the absence of the hydatid thrill and other typical symptoms will avoid error. A projecting and enlarged gall-bladder is sometimes simulated by an adrenal tumor capable of displacing the intestines anteriorly; but the latter are much less tense than such a gall-bladder. Abdominal aneurism may be suggested, but the absence of aneurismal bruit and the absence of all other signs of adrenal growth eliminate this source of error. In renal cancer or renal hypernephroma, hæmaturia and other evidences of renal disorder are usually present, while they are more likely to be absent in malignant growths of the adrenals. Pain occurs earlier than in renal tumors, while febrile disturbance is rare in the latter.

Two symptoms, according to Israel,[221] point to involvement of the suprarenal gland: (*a*) Paroxysms of pain and paræsthesias in the absence of a palpable tumor, and (*b*) a febrile course.

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[221] Israel: Deut. med. Woch., No. 44, 1903.

The painful paroxysms in renal as well as suprarenal tumors are due to the extension of the neoplasm to the roots of the lumbar plexus. In suprarenal tumors this may occur quite early owing to the immediate vicinity of these structures. On the other hand, in renal tumors the invasion of the capsule usually takes place at a late period when the growth has reached so considerable a size as to become palpable. The fact that fever occurs in cases of suprarenal tumors has hitherto been unknown. Israel observed it in 57 per cent. of his cases, while in renal tumors it was present only in 1 to 2 per cent.

Another apparently characteristic fact in differentiating from renal tumor is that the adrenal growth tends to approach more nearly the median line (in the region from the seventh to the ninth costal cartilages), while the primary tumor of the kidney appears first in the region from the ninth to the eleventh. Tumor of the adrenal at the time of its presentation beneath the margin of the ribs appears broader than does that of tumor of the kidney, and the lower contour of the tumor of the adrenal is much less rounded than is that of the kidney.

The emphasis laid by Israel on the presence of fever in adrenal malignant neoplasms affords striking proof of the correctness of my contention, urged ever since 1903, that the adrenals, through the rôle of their secretion in oxidation and metabolism, were the active organs in fever—a process which pathologists have failed to explain.

Leucocythemia is sometimes simulated; but the absence of myelocytes and other characteristics soon eliminate this disease.

Ecchymosis of the orbit of unaccountable origin in infants and young children or tumor of the orbit should cause careful search for manifestations of malignant tumors of the adrenals, as previously stated.

TREATMENT.—Removal is the only resource, but as a rule the result is unsatisfactory owing to the fact that the presence of the growth is recognized only through metastasis; or when it has developed to a marked extent, and produced either through metastasis, pressure, etc., disorders in other parts of the organism which cannot be reached.

Cases in which the tumor involves one adrenal only, as suggested by the absence of symptoms of adrenal insufficiency, marked asthenia, emaciation, hypothermia, etc., and the presence of a tumor and hyperæsthesia on one side only, offer a better chance of success, since they indicate that the other adrenal will probably be able to subserve alone the needs of the organism. The chief difficulty encountered in the course of the operation is a marked tendency to hæmorrhage owing to the friability of the morbid tissues.

CHAPTER III.

THE THYROPARATHYROID APPARATUS IN GENERAL OXIDATION AND IMMUNITY.

We can no longer speak of the thyroid gland as a functional entity. The two external parathyroid glandules, discovered in 1880 by a Swedish physician, Sandström, and the two internal parathyroid glandules, discovered by Nicolas,[1] of Nancy, in 1893, and independently by Kohn,[2] of Prague, in 1895, introduced a new era in our conception of this organ. Foreign investigators, therefore, tend increasingly to adopt the term "thyroparathyroid apparatus" owing mainly to the anatomical relationship between the glandules and the thyroid vessels, with which their own circulation is directly connected. We shall see, however, that many physiological facts, the first of which were pointed out by Gley, of Paris, in 1892, and clinical observations warrant the use of this compound term.

PREVAILING VIEWS AS TO THE FUNCTIONS OF THE THYROID AND PARATHYROIDS.

In 1859, Shiff, of Geneva, found experimentally that removal of the thyroid gland in the dog caused violent nervous disorders and death. Two surgeons of the same city, the brothers J. L. and A. Reverdin, then pointed out (1882) that in certain goitrous subjects, and after the complete removal of goiter in otherwise normal subjects, there also appeared marked trophic and nervous disturbances. This was confirmed the following year by another Swiss surgeon, Kocher. The principal postoperative phenomena noted were: marked weakness and fatigue, a sensation of cold, pallor, muscular stiffness, and pains; œdematous thickening and pallor, hardness and dryness of the skin, the normal folds being more or less effaced, and loss of hair. The main nervous and mental phenomena were: tetany, sometimes attaining the violence of true tetanus and passing into clonic convulsions. The intelligence was also diminished, with slow intellection and enunciation as characteristic features. Paroxysms of suffocation, vertigo, syncope occurred, followed by death within a period varying from four to nine days in the vast majority of cases, the fatal ending being sometimes delayed two or three weeks beyond this period.

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[1] Nicolas: Bull. de la Soc. des Sci. de Nancy, vol. v, p. 13, May 3, [illegible].
[2] Kohn: Archiv f. mikrosk. Anat., Bd. xliv, S. [illegible], 1895.

The brothers Reverdin termed this condition *postoperative myxœdema,* while Kocher called it *cachexia strumipriva.* The term *myxœdema* had already been attributed (1877) by Ord to the, now familiar, disease of which thyroid insufficiency is the predominating pathogenic factor, and which Sir William Gull had, in 1873, called "a cretinoid change."

The same phenomena were observed in the monkey by Horsley, in 1885. This observer and many others also found that the symptoms were most severe in carnivorous animals; somewhat less so in man and in the monkey; still less so in ruminants and undulates, and that they failed to occur in birds and rodents. But these experimental dissimilarities were to a great extent obliterated by the subsequent experiments of Gley, de Quervain, Hofmeister, Edmunds, and others, which showed that the variations depended mainly upon the anatomical relationship of the parathyroids and the thyroid. Thus Gley, of Paris, found, in 1892, that in the rabbit two of the four parathyroids were situated below the thyroid and were, therefore, not removed with the thyroid; while in the dog, all four parathyroids are so imbedded in the latter that it is only with great care that they can be left *in situ.*

Gley discovered another important fact: he showed that, while removal of the thyroid alone does not necessarily cause death, it was the removal of the four parathyroids which caused the nervous phenomena and the fatal ending. These observations have been sustained by many investigators, who have gradually accounted for many phenomena attributable to each organ, as will be shown in the following pages.

Removal of the thyroid only, produces morbid phenomena the severity of which depends upon the age of the animal; the younger the animal, the greater are the morbid effects witnessed, though life itself is not necessarily endangered. The animal fails to grow. The bones and epiphysial cartilages fail to develop, the skull alone escaping; the abdomen projects and becomes larger, though relatively flabby. The testicles remain small and may fail to descend; the ovaries are also, as a rule, atrophied.

Sterility due to the non-formation of semen has been noted. Pregnant rabbits abort; hens produce very small eggs or none at all. The animal is apathetic, indifferent, dirty, awkward and apparently devoid of intelligence, and quite recalls the human cretin. The skin is rough, coarse, and squamous, being, in some, considerably creased, as in the aged, and, in others, swollen, hard, and resistant, as in myxœdema. The hair becomes coarse and shaggy, losing all luster, and tends to grow irregularly and fall. The temperature, normal at first, steadily decreases until death, the respiratory exchanges and oxidation being diminished, the nitrogen excretion likewise showing, clearly, inhibited metabolism. Anæmia, with reduction of the red corpuscles, is marked. Paralysis and convulsions may appear, but, as a rule, the animal dies cachectic after a prolonged period, the development of the trophic disorders being slow—two or three months in the most rapid cases—*i.e.*, the youngest, according to Jeandelize.

As observed by Charrin, and as will be shown later in this chapter, removal of the thyroid reduces the resistance to infections, and also, according to Lindemann, to intoxications. In man the postoperative phenomena, *i.e.*, cachexia strumipriva, rarely appears before three or four months and occasionally after a year. The same vulnerability to infections is also prominent and the sufferers are often carried away by an intercurrent infection, especially tuberculosis and pneumonia.

In full-grown subjects no marked physical changes occur, but nutrition is nevertheless impaired, emaciation, anæmia, coarseness of the skin, falling of hair, hypothermia, and other manifestations of myxœdema manifesting themselves. These phenomena are aggravated by pregnancy and lactation, repeated pregnancy and prolonged lactation having in fact been found by Morvan to favor the development of myxœdema irrespective of thyroidectomy.

On the whole, removal of the thyroid gland alone gives rise in the young: 1, to arrested growth especially marked in the skeletal bones and sexual organs; 2, to myxœdematous thickening of the skin; and 3, to a low grade of intelligence with general apathy—as main morbid phenomena, constituting the syndromes recognized under the term cretinism; while in the full grown it causes the condition known as myxœdema.

Removal of the Parathyroids Only.—Removal of the thyroid and parathyroids causes early death, while removal of the thyroid alone, we have just seen, is followed by a prolonged postoperative life. It is to the removal of these diminutive organs, in fact, that all the nervous phenomena must be ascribed. Even when the thyroid is left *in situ,* and the four parathyroids are removed, we witness a typical syndrome: The predominant feature of the syndrome is the tendency to spasm and convulsions which may range from tetany to violent tetanic or epileptic paroxysms, with foaming at the mouth, during which the subject may die, owing to spastic immobilization of the thoracic muscles. Fibrillary tremors, tetanic and choreic movements, sufficiently violent in some cases to throw the patient to the floor are also observed. As in strychnine poisoning, the least contact evokes contractures and convulsions. Marked dyspnœa, the dominant symptom in rabbits, and paroxysms of suffocation occur both during and after the latter. The respirations are greatly accelerated, 100 to 200 times a minute in animals. Although the temperature rises during the convulsive paroxysms, it goes down considerably during the intervals, both the external and internal temperature being 4° C. or more below normal and gradually receding as death approaches. Oxygenation is deficient; the blood contains less oxygen; the red corpuscles are reduced, though the polynuclear leucocytes are increased; cyanosis is clearly shown in the rooster's comb and in the monkey. The pulse, slowed during the intervals, becomes extremely rapid and tumultuous during the convulsions. Involvement of the alimentary canal is shown by ptyalism, fœtid breath, anorexia, the animal being also liable to spasm of the masseters when he attempts to take food, marked thirst, bilious and mucous vomiting, fœtid diarrhœal and bloody stools. Although the animal appears weak, somnolent, and indifferent to its surroundings, as a rule, it is sometimes terror-stricken and agitated, and seems to suffer. Pruritus is an evident symptom. The urine is greatly reduced and abnormally toxic, especially during the convulsive and dyspnœic paroxysms; it is also markedly spasmogenic when injected into another animal. Albumin and glucose are often present; indican likewise; the chlorides and the potassium salts are present in excess; the pigments and biliary salts likewise, though their ratio tends gradually to lessen. Urea and phosphates are diminished.

These morbid effects usually begin about twenty-four hours after removal of all the parathyroids. In dogs, a single parathyroid of the four suffices in most instances to carry on their functions, but even two of them will fail to do so in some animals, removal of the other pair being followed by tetany. Death usually occurs in from three to five days after removal of all four organs; though, rarely, it does not occur until much later, forty-five days in some instances. The possibility of supplementary organs is, of course, not to be overlooked under such circumstances. As many as six parathyroids have been found at autopsies. Auerbach[3] recently found five in an infant, but only two in 5, and but one in 8. These 13 children all showed a tendency to spasm.

Dual Function Theory.—Gley having shown the vast importance of the parathyroids, he concluded that their purpose was to supplement the function of the thyroid. The fact that the parathyroids became atrophied on removal of the latter seemed fully to sustain this view. Additional proof was seemingly afforded by the continuation of life for some time after the same procedure, the parathyroids being thus shown capable of carrying on the functions of the thyroid independently.

Contrary to this conclusion, however, was the fact, noted by Moussu and verified by Gley and also Nicolas, that the parathyroids, which became hypertrophied after removal of the thyroid, never assumed the histological structure of the latter, but retained their own. Moreover, as emphasized by Moussu, in 1893, experimental evidence pointed to the presence of two functions. This view was sustained by the discovery of two investigators, Nicolas and Kohn, working independently, of the two additional parathyroids, two only having been described by Landström, as previously stated. These two glands sufficed to maintain life after the thyroid and parathyroid had been removed. Vassale and Generali now obtained in the dog the complete effects of removal of the whole thyroid apparatus by extirpating only the four parathyroids, a result confirmed in the rabbit by Rouxeau. Moussu then showed that extirpation of the thyroid alone was practically harmless in adult animals, but that in very young animals it was followed by experimental cretinism, while removal of the parathyroids gave rise to the nervous phenomena described in all animals, excepting, perhaps, the ox and horse.

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[3] Auerbach: Jahrbuch für Kinderheilkunde, B. lxxxiii, Suppl., 1911.

On the whole, the prevailing view is that the parathyroids are functionally independent of the thyroid. We shall see, however, that many facts militate against this conclusion.

Effects of the Internal Secretion of the Thyroid.—Various theories as to the manner in which the thyroid carries on its functions have been vouchsafed, but all have succumbed to the view that the organ secretes some substance which finds its way into the blood, *i.e.*, that it produces an internal secretion. This was suggested a century ago by the experimental work of King, of London, who found that the colloid substance of the gland passed into the lymphatics, an observation confirmed by Hurthle, Baber, Sir Victor Horsley, and others.

That the organ is a secreting one is shown by the fact that it can be transplanted or grafted from its normal site to other parts of the body. Grafting was first successfully performed by Schiff, and repeated by many other investigators, including von Eiselberg, but notably by Christiani, of Geneva. Very uncertain at first, the method was, however, so perfected by the latter experiments that success now attends every operation. It consists in inserting not a whole lobe, as had been previously practised, but small fragments. After a time there is produced *in situ* a nest, as it were, of typical thyroid tissue capable of carrying on the functions of the original gland. Moreover, this tissue seems capable of doing by means of its secretion what the thyroid tissue proper cannot do, viz., to protect the animal against tetany. Louis Morel[8a] recommends intraperitoneal, intrasplenic and intraosseous grafts as the most satisfactory.

Again, extracts of the gland, the gland itself, in its raw state or desiccated, antagonize the morbid effects of thyroidectomy. This was first shown by Vassale, who found that the intravenous injection of aqueous extract of thyroid controlled temporarily these phenomena. This experiment was the starting point of Murray's memorable introduction of the use of thyroid preparations in myxœdema in all its forms. In toxic doses, thyroid extract was found by Ewald, Fenwick, Haskovec, and many others to cause: rapid emaciation, marked vasodilation, a rapid pulse, diuresis, acceleration of the lymphatic circulation, hypothermia, polypnœa, polyphagia, polydipsia, glycosuria, excessive excretion of nitrogenous wastes, soon followed by extreme depression, anorexia, vomiting, loss of reflexes, paralyses, convulsions, and death—all phenomena which may be evoked in man by injudicious thyroid medication.

[8a] Louis Morel: Archives génér. de chirurgie, May, 1912.

A feature worth retaining, in view of conclusions to be submitted later, is that many observers, including Treupel, Ord, and Ver Ecke, have laid stress upon the correlation of the thyroid functions with general nutrition. Not only is there increased elimination of nitrogenous and other tissue wastes, but, as emphasized by Magnus-Lévy, the respiratory exchanges, including, of course, the intake of oxygen, are greatly increased. Moreover, Vassale and Generali[4] advanced the view, quite compatible with all these biochemical observations and with the known effects of the thyroid extracts in cretinism and myxœdema, that the thyroid secretion served to activate metabolic processes, both in the cutaneous tissues and in the organism at large.

Effects of the Internal Secretion of the Parathyroids.—Removal of these organs being followed by spasm and convulsions, the normal conclusion at once suggested itself that their purpose was to destroy spasmogenic poisons produced within the body. Indeed, the blood of dogs subjected to parathyroidectomy was found by Rogowitsch and others to be toxic and to cause convulsions in normal animals, while Laulanié and others found the urine also toxic. The liver, according to Morel and Rathery,[5] shows acidosis degeneration, while Morel[5a] and Werelius[5b] found that parathyroidectomy enhances the liability of pregnant animals to autotoxic convulsions.

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[4] Vassale and Generali: Arch. ital. de biol., vol. xxxii, p. 154, 1900.
[5] Morel and Rathery: Jour. de physiol. et de path. gén., Sept., 1912.
[5a] Morel: La gynécologie, April, 1912.
[5b] Werelius: Surgery, Gynecol. and Obst., Feb., 1912.

The injection of parathyroid extract was found to antagonize the convulsive disorders caused by the extirpation of all parathyroids by Moussu and other observers, but the beneficial effects lasted a short time only, the animals dying nevertheless. As shown by Vassale, the same beneficial effects are obtained by the injection of thyroid extract. Transfusion of a normal dog's blood to that of one deprived of its thyroid and parathyroids was also shown by Fano and Zanda to palliate considerably the convulsive phenomena. Still, the fact that parathyroid extract arrests the latter temporarily has generally been accepted as proof that the parathyroids contribute independently of the thyroid some antitoxic substance to the blood.

Of experimental and clinical interest in this connection, however, are the observations of Macallum and Voegtlin,[5c] and Macallum,[5d] that calcium salts given by the mouth or hypodermically inhibit the tetany due to removal of the parathyroids, both in man and in lower animals, apparently restoring them completely. This suggests that it is by influencing in some way calcium metabolism that the parathyroid secretion produces its antitoxic effects.

OBSCURE FEATURES OF THE THYROPARATHYROID PROBLEM.

As the foregoing review of the status of the question indicates, much valuable work has been contributed toward its elucidation. Yet if we ask what the functions of the thyroid and parathyroids are in the economy, it must be admitted that none of the data or conclusions available answer the question. Growth and mental development are prevented by arrest, either through organic inhibition of the functions of the thyroid or through removal of this organ. What function does it carry on that enables it to influence so fundamentally the welfare of the entire organism? Vassale's view that the thyroid secretion serves to hasten tissue metabolism is a self-evident conclusion sustained by the symptomatology of and the use of thyroid preparations in myxœdema and cretinism, but it does not tell us *how* it fulfills this function, *i.e.*, what its secretion does to incite and sustain it.

[5c] Macallum and Voegtlin: Johns Hopkins Hosp. Bull., Mar., 1908.
[5d] Macallum: Jour. of the Am. Med. Association, Aug. 3, 1912.

In the preceding chapter, I filled the corresponding gap in respect to the adrenals by tracing the adrenal secretion to the pulmonary alveoli, and showed that it was converted into adrenoxidase in this location, and that it served, through the intermediary of the red corpuscles, to sustain oxidation, metabolism, and nutrition. What is the corresponding itinerary of the thyroid secretion? Accepting the prevailing and irrefutable view that the latter does sustain metabolism, what is the functional relationship between the thyroid and the adrenals? Again, we find that removal of the thyroid, as does that of the adrenals, predisposes greatly to infection. In virtue of what property does the thyroid secretion contribute to the protection of the body against infectious diseases? These and many other questions have not as yet been answered.

The field of the parathyroids is at least as replete with obscure factors. The same lack of knowledge concerning the itinerary of their secretion, its relationship with the blood, and the actual rôle it fulfills prevails. The salient postoperative effects being convulsive disorders of various types, we are again brought to the necessity of attributing to these organs a very active participation in the autoprotective resources of the body, the poisons antagonized being no longer toxins, but, apparently at least, toxic products of metabolism, *i.e.*, spasmogenic intermediate wastes. Here, again, we find ourselves confronted with an active sway over metabolism or, better perhaps, catabolism. Indeed, the importance of this attribute is of major importance in the practical field. As Parhon and Golstein[6] write: "Certain pathological states, such as pregnancy, parturition, lactation, certain disorders of the female genital apparatus, certain diseases of the thyroid, can facilitate the appearance of tetany, which under these conditions is probably of parathyroid origin." As to the present status of the question, the same authors conclude (1909) "that the intimate mechanism of the production of parathyroid tetany—as well as other forms of tetany—has not as yet been elucidated. The data we possess for the time being cannot but indicate the path that researches still necessary should follow to solve the question."

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[6] Parhon and Golstein: "Les Sécrétions Internes," p. 200, Paris, 1909.

THE THYROPARATHYROID SECRETION AS AN OXIDATION ACTIVATOR THROUGH ITS ACTION ON CELLULAR PHOSPHORUS.

Verworn,[7] referring to Max Schultze's observation that the phosphogenic cells of lightning bugs absorb oxygen actively, quotes approvingly Pflüger's statement concerning this process: "Here, in the wonderful spectacle of animal phosphorescence, nature has given us an example that shows where the taper burns that we call life." If, on the other hand, we recall Hutchison's[8] remark: "Briefly then, it may be said that the effect of the administration of the thyroid is to increase oxidation in the body; it makes tissues, as it were, more inflammable, so that they burn away more rapidly" and also the fact that iodine when brought into contact with phosphorus causes ignition of the latter, the meaning of the above heading will be apprehended. Briefly, from my viewpoint, *the iodine in organic combination which the thyroparathyroid secretion contains renders the phosphorus of all tissue cells, and particularly their nuclei, more prone to undergo oxidation by the adrenoxidase of the blood.* Hence the great influence of the thyroid gland on oxidation, on the vital process itself, on development, physical and mental, as is well shown by the results of thyroid preparations in cretinism and other kindred disorders.

In the earlier editions of the present work, I advanced the view that it was in part through the adrenals that the thyroid secretion produced its effects, and that, conversely, "cachexia strumipriva," *i.e.*, the myxœdema which follows removal of the thyroid, was "partly a consequence of adrenal insufficiency." This view, which makes oxidation the common aim of two sets of organs, suggests itself when the effects of extirpation of the thyroid are compared with those following removal of the adrenals. Both postoperative syndromes include central and peripheral hypothermia, lowering of the blood-pressure, dyspnœa, cyanosis, accelerated respiration, weakness and increased rapidity of the heartbeat and pulse, muscular weakness, mental torpor, melancholia, muscular rigidity, convulsions, coma, and death; even bronzing is sometimes witnessed in the advanced stages of myxœdema. Conversely, the effects of thyroid preparations strikingly recall those awakened by the adrenal secretion. Beebe,[9] for example, while acknowledging that it is not known "on what tissue or set of tissues the thyroid secretion acts," states: "We know that it is connected in some way with the function of oxidation in the body. By the administration of thyroid to a cretin or a patient with myxœdema, it is possible to increase the absorption of oxygen from 20 to 75 per cent. There is a corresponding increase in the amount of heat given off from the body. The removal of the thyroid in an animal will cause diminution in the absorption of oxygen, which may be again increased by thyroid feeding. Administration of thyroid to a normal animal will cause an increase of from 10 to 40 per cent. in the oxygen demand."

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[7] Verworn: "General Physiology." Amer. ed., p. 265, 1899.
[8] Hutchison: Brit. Med. Jour., July 16, 1898.

All this naturally suggests a mutual stimulation between the thyroparathyroid apparatus and the adrenals. In 1903, I advanced the view that the thyroid secretion directly or indirectly increased the adrenal secretory functions.

Experimenters who have taken up the question have also been led independently to the conclusions I had previously reached.[10] That experimental thyroidectomy should produce no histological changes in the adrenals, as was observed by Hofmeister,[11] Bensen,[12] Bruckner,[13] and others, is self evident, unless the adrenals be endowed with compensative functions, which has never been demonstrated. But it is when hyperactivity of the thyroid is used as the basis of the inquiry that such a functional relationship between the two sets of organs shows itself. While, for example, normal blood has no mydriatic power, injections of thyroid extract confer this property of the adrenal secretion upon it, owing, according to Kraus and Friedenthal[14] and Caro,[15] to stimulation of the adrenals. Kostlivy[16] also observed in a large number of cases of thyroid intoxication that the blood-serum produced dilatation of the pupil, while thyroidectomy caused this power markedly to decline. The same mydriatic activity was conferred on the serum of animals by giving thyroid extract by the mouth, the mydriatic power corresponding with the dose administered. Hoskins,[17] who refers to the above observations, obtained similar results in guinea-pigs. In both exophthalmic goiter and myxœdema, as we shall see, the participation of the adrenals in the processes shows itself in various ways. Physiology and clinical medicine thus unite in showing that the secretion of the thyroid apparatus enhances the functions of the adrenals. I might, however, express this in a different term. Starling[18] has named "hormone" (from ὁρμαω, arouse or excite) a substance which, originating in one organ, is capable of stimulating another. Internal secretions being included among the hormones, we can state that the hormones produced by the parathyroid apparatus are capable of stimulating the adrenals. That the thyroid secretion does not serve only for this purpose, however, is suggested by the fact that it is component of the blood at large. We can only, therefore, look upon its exciting effect upon the adrenals as an incidental feature of a general function.

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[9] Beebe: Jour. of the Amer. Med. Assoc., Mar. 4, 1911.
[10] Sajous: "Internal Secretions and the Principles of Medicine," vol 1, 1st ed., p. 152, 1903.
[11] Hofmeister: Beiträge z. klin. Chir., Bd. xi, S. 463, 1894.
[12] Bensen: Virchow's Archiv, Bd. clxx, S. 229, 1902.
[13] Bruckner: Comptes-rendus de la Soc. de biol., vol. lxiv, p. 1123, 1908.
[14] Kraus and Friedenthal: Berlin klin. Woch., Bd. xlv, S. 1710, 1908.
[15] Caro: Med. Klinik, Berlin, Bd. vi, S. 136, 1900.
[16] Kostlivy: Mitt. a. d. Grenzgeb. d. Med. u. Chir., Bd. xxi, Nu. 4, 1910.

What is the nature of this function? We have seen that the prevailing views afford no answer to this question. We are, therefore, brought back to the answer I submitted at the beginning of this section, viz., that "iodine in organic combination which the thyroparathyroid secretions contain renders the phosphorus that all tissue-cells and particularly their nuclei contain more prone to undergo chemical change, *i.e.*, oxidation in this connection, with the adrenal product adrenoxidase as its source of oxygen," and to analyze the evidence which led me to it. The plan adopted for the same purpose in the case of the adrenals will be carried out, viz., to submit the main evidence in detail, though in as terse a form as possible. Starting with the nature of the thyroparathyroid secretions, I shall then trace their itineraries throughout the organism as an organic compound, and finally its function.

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[17] Hoskins: Amer. Jour. of Physiol., vol. xxvi, p. 426, 1910.
[18] Starling: "Recent Advances in the Physiology of Digestion," 1906.

The thyroid product is an "iodized globulin" (as Oswald maintains), the globulin being the albuminous constituent of hæmoglobin, i.e., *adrenoxidase.*

As Notkin[19] and also White and Davies[20] hold, the action of the thyroid secretion resembles that of an organized ferment. The identity of this ferment suggests itself, *i.e.*, the adrenal active principle, when we consider Baumann's analyses of his thyroidin. Among other tests, for example, he found that it was practically insoluble in ether and chloroform; that it was not destroyed by digestive ferments, and that it stood a temperature of 100° C.[21] These are the specific tests of adrenalin. That this active principle, in turn, occurs as a constituent of what I have termed "adrenoxidase," is shown by the fact that it also gives the tests of the plasmatic oxidase; Lépinois, for example, found that the thyroid secretion contained an oxidase which gave the blue reaction with tincture of guaiac. Again, we have seen that adrenoxidase is a globulin: Oswald termed his product "thyroglobulin" and described it as an "iodized globulin." Again, adrenoxidase being the oxidizing constituent of the blood, and circulating as it does in all tissues and organs, as the albuminous portion of the hæmoglobin, it must necessarily circulate also in the thyroid and parathyroids as a blood constituent, and out of which the secretions of these organs obtain it.

The actual presence of an oxidizing ferment was further confirmed recently by Youchetchenko.[22] Under the heading of "oxidizing ferments" of the thyroid gland, he states that this organ is "rich in catalases." As I have shown in the preceding chapter, catalysis is a property of the adrenal active principle. He found, moreover, that "the catalase, as well as the oxidizing ferment, is contained in the red blood-corpuscles." This corresponds precisely with the fact I pointed out several years ago in the first edition of the present work. In keeping also with what I had held concerning the influence of the thyroid on oxidation (partly through its influence over the adrenals), Youchetchenko found that in dogs "thyroidectomy was invariably followed by a manifest, at times considerable, lowering of the temperature"; "in two dogs," he adds, "this oxidizing power fell almost to one-half of the normal."

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[19] Notkin: Wiener med. Woch., Bd. xlv, S. 824 u. 872, 1896.
[20] White and Davies: Cited by Halliburton: Practitioner, Jan., 1897.
[21] Cited by Morat and Doyon: Traité de physiologie, vol. i, p. 467, 1904.
[22] Youchetchenko: Archives des Sciences Biologiques de l'Institut Impérial Médecine Expérimentale à St. Petersburg, Tome xv, Nos. 3 and 4, p. 173, 1910.

Yet in the light of the functions I have ascribed to the adrenals, and the functional stimulation these organs receive from the thyroid product, these effects upon the temperature should correspond with a reduction of the oxyhæmoglobin, the active agent of which is adrenoxidase. That such is the case is shown by the experiments of Albertoni and Tizzoni,[23] who found that removal of the thyroid caused the blood to show *decreased power to fix oxygen;* while Masoin[24] found that the relative quantity of *oxyhæmoglobin* in the blood was diminished gradually as the postoperative phenomena of thyroidectomy progressed.

Another constituent of thyroidin may be regarded much in the same light, viz., nucleoproteid. Sherrington, Milroy and Malcolm,[25] and others have found that the granulations of the most numerous leucocytes in the blood, the neutrophiles, are composed of nucleoproteid, while the observations of Bail, Stokes, and Wegefarth,[26] Sangree,[27] and others have as clearly shown that these granulations leave the periphery of the cell. We shall see in the next volume that it is through these cells that nucleoproteid reaches the thyroid apparatus.

E. C. Kendall[28] of the Mayo Clinic, has isolated from the gland a crystalline substance he has termed "thyroxin," which contains no less than sixty per cent. of iodine, and possesses the physiological activity of the gland proper. It is thought to act[28a] by the deamination of amino-acids. The products are then used for the formation of carbohydrates, fats, etc. This does not, however, meet the results of clinical observation in hyperthyroidism or Graves's disease in which a marked increase of phosphoric acid excretion is observed. Be this as it may, Kendall's thyroxin is a valuable addition to the list of thyroid derivatives at our disposal.

That iodine is the active agent of the thyroparathyroid secretions is now absolutely established. Some observers have held that the thyroid and parathyroids contain no iodine, in opposition to the findings of many authorities, but this must be ascribed to defective analytic work. Beebe, while stating that "the physiologically active portion of the gland secretion is a protein substance containing iodine in a specific organic combination," also remarks: "I have never been able to obtain a definite protein or proteose from the thyroid absolutely free of iodine." Quantities of iodine varying from 2.05 to 13.04 mg. per gland have been found by Baumann, Weis, Oswald, Rosetzki, Iolen, Gley, and others, in Europe, and Wells (10.79 mg.), in this country. Moreover, "if potassium iodide be given to an animal, there is an increase in the content of the physiologically combined iodine in the gland." As Oswald holds, therefore, the thyroid product is an "iodized globulin."

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[23] Albertoni and Tizzoni: Cited by Maragliano: Gaz. degli Ospedali, Oct. 30, 1894.

[24] Masoin: Bulletin de l'Académie de Médecine de Belgique, No. 1, p. 88, 1896.

[25] Milroy and Malcolm: Jour. of Phys., vol. xxv, p. 106, 1899.

[26] Ball, Stokes, and Wegefarth: Bull. Johns Hopkins Hosp., Dec., 1897

[27] Sangree: Phila. Med. Jour., Mar. 12, 1898.

[28] Kendall: Jour. Amer. Med. Assoc., vol. lxvi, p. 811, 1916.

[28a] Kendall: *Loc. cit.*

Again, as stated by Parhon and Golstein[39] in a general review, referring to the identity of the thyroid product, "Fortunately we are today better informed concerning the functions of the thyroid body, and if we cannot exclude the production of certain enzymes by the thyroid cells we can, on the other hand, affirm that their principal action is due to a more clearly defined substance, which is an iodized globulin."

The foregoing analysis has shown that in keeping with the prevailing view the active principle of the thyroparathyroid secretions is iodine; but inasmuch as its activity in this organic combination exceeds greatly that of iodine or its salts, a property which its combination with a ferment (adrenoxidase) explains, its true identity is more accurately expressed by the term "*thyroiodase,*" which I suggested some years ago.

Why should this combination occur? We will see presently that its purpose is primarily to insure the absorption of the iodine by the red corpuscles, hæmoglobin being the normal host of these cells. Analysis of this question showed that

The thyroid and parathyroid secretions ultimately reach the superior vena cava and are carried to the pulmonary alveoli, where they combine and are taken up by the red corpuscles, along with the adrenal secretion.

King, over a century ago, traced the thyroid secretion to the lymphatics, and Hürthle showed that fluids as well as their colloid passed from the thyroid vesicles to these vessels, a fact confirmed by Horsley and others. Baber found colloid similar to that in the thyroid within the lymphatic vessels. The more recent investigations of Biondi,[30] Zielinska,[31] Vassale and de Brazza[32] on the thyroid, and those of Welsh,[33] and Capobianco and Mazziato,[34] and others on the parathyroids, have shown that the product of these organs passes into the perivascular lymph-spaces. Being then transferred to the larger cervical lymphatics, they are discharged by the right and left lymphatic ducts—the thoracic duct, according to Pembrey[35]—into the subclavian veins, and by way of the superior vena cava to the heart. Here they become merged with the venous blood of the entire organism, *forming a single secretion,* which is then inevitably carried to the heart, and thence to the lungs. As the venous blood carrying the adrenal secretion passes from below to these organs to be oxygenized, so is the thyroparathyroid secretion carried from above to the air-cells.

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[39] Parhon and Golstein: "Sécrétions Internes," p. 18, Paris, 1909.

All these facts tend to controvert the current view that the thyroid and parathyroids are not functionally related. The fact is that the prevailing opinion, referred to on p. 147, is not based on a broad view of the evidence in the case. My own conception sustains and completes that of Gley, which admits a functional association in the sense that one set of organs serves to complete the work of the other. This intimate connection is shown by the observation of Edmunds that, while extirpation of the parathyroids causes histological changes in the thyroid, removal of the latter also causes degeneration of the parathyroids. Moreover, Vassale and Generali[36] found that after death from removal of the latter the thyroid contained no colloid. Lusena[37] noted the same fact, thus showing that the formation of the thyroid secretion depends in some way upon the functions of the parathyroids. Edmunds emphasized this fact by showing that hypertrophy of the thyroid followed parathyroidectomy, both embryonic tissue and vessels showing development. This survival suggests that removal of the parathyroids is not as fatal as generally believed. Indeed, Gley[38] had two dogs survive removal of all the parathyroids leaving only one lobe of the thyroid; the same operation in two other dogs and in a cat was followed by disturbances which became fatal on removing the remaining thyroid lobe. In another dog parathyroidectomy caused only trophic disturbances and death in one month. The same thing was observed in rabbits when two parathyroids only were left. Edmunds[39] also had two survivals in dogs after parathyroidectomy and deems this operation less grave than thyroidectomy, an opinion which is also Gley's.

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[30] Biondi: Berl. klin. Woch., Bd. xxv, S. 954, 1888.
[31] Zielinska: Virchow's Archiv, Bd. cxxxvi, S. 170, 1894.
[32] Vassale and de Brazza: Arch. ital. di biol., vol. xxiii, p. 292, 1895.
[33] Welsh: Jour. of Anat. and Physiol., Apr., 1898.
[34] Capobianco and Mazziato: Giorn. Int. de Sci., Nos. 8, 9, and 10, 1899.
[35] Pembrey: Hill's "Recent Advances in Physiology," p. 579.
[36] Vassale and Generali: Riv. di Patol. Nerv. et Ment., vol. i, pp. 95 and 249, 1896.
[37] Lusena: Fisio-patologia dell'Appar. Tiro-parat.. Florence, 1899.

Again, Halpenny,[40] after a comprehensive series of experiments in the same direction, writes: "I have been unable to confirm the statement that complete parathyroidectomy invariably proves fatal, and that in a short time. In dogs 3 and 7, where serial sections of the thyroid removed post-mortem showed no parathyroid, the animals lived 30 and 27 days, respectively, without symptoms and were killed. In dog 1, symptoms did not occur, and at the post-mortem no parathyroids were found, although serial sections were not cut. In cats 1, 6, and 8, in which at the operation the thyroid lobe with the parathyroids on one side, and the parathyroids alone on the other side, were removed, the animals lived, without symptoms, 23 days, 25 days, and 30 days, respectively, and were then killed. In all three cases a careful post-mortem search was made, and the remaining lobe of the thyroid was cut in serial sections, and no traces of parathyroid was found. There is a tendency to disregard these exceptions—MacCallum and Davidson,[41] Berkeley and Beebe[42]—and explain them by supposing that parathyroids have remained behind unobserved." This explanation is hardly tenable in view of the numerous examples presented. As to accessory glands, as Vincent[43] states, "If accessory glands be so usually present, the question as to the importance to life of these glands ceases to have the value hitherto attached to it." Although I believe Halpenny killed his animals too soon after the operation, Parhon and Golstein[44] having observed postoperative death (though without tetanic phenomena) as much as 30 and 66 days after thyroparathyroidectomy in the cat, the fact remains that added to the data recorded by Gley his evidence tends to weaken the view that the parathyroids are endowed with independent functions. Swale Vincent, in his recent book (1913), adduces convincing data indicating "an intimate relationship between the two structures," anatomical, physiological, and pathological.

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[38] Gley: Brit. Med. Jour., Sept. 21, 1901.
[39] Edmunds: Jour. of Pathol. and Bacteriol., Jan., 1896.
[40] Halpenny: Surgery, Gynecology, and Obstetrics, May, 1910.
[41] MacCallum and Davidson: Medical News, Apr. 8, 1905.
[42] Berkeley and Beebe: Journal of Medical Research, Feb., 1909.
[43] Vincent: London Lancet, Aug. 11 and 18, 1906.

Finally, and pointedly suggesting a combined function, we have seen that a transplanted or grafted piece of thyroid tissue, free of all parathyroid tissue, assumes the functions of both sets of organs, arrests the convulsive disorders due to extirpation of the parathyroids alone, and prevents death.

All this clearly points to a functional connection (probably a nervous one to co-ordinate the relative proportions of their secretions) between these two sets of organs, and thus insures the ultimate formation in the lungs of a perfect, *i.e.*, physiological, thyroparathyroidal product.

The purpose of this itinerary suggests itself when we recall that, as stated by Nothnagel and Rossbach,[45] hæmoglobin can fix large quantities of iodine. It accounts also for the fact that Gley[46] and Bourcet found iodine in the red corpuscles. Being a component of the albuminous hæmoglobin of these cells with adrenoxidase, however, iodine should be found in all tissues. While Bourcet[47] ascertained that such was the case, Justus[48] found it in all cellular nuclei, so rich as is well known in phosphorus. This simultaneous presence of iodine and phosphorus in the nuclei, and also of iodine in the red corpuscles, suggests the nature of process carried on in the cells: viz.,

The thyroparathyroid constituent of the hæmoglobin enhances oxidation by increasing, as a ferment, the vulnerability of the phosphorus, which all cells, particularly their nuclei, contain, to oxidation by the adrenoxidase in the blood.

This action is strikingly shown by the fact that iodine, the active constituent of the thyroid secretion, and its salts, as shown by Henrijean and Corin,[49] Handfield Jones,[50] and others, cause excessive elimination of phosphates and phosphoric acid, and that thyroid preparations, according to Roos, Scholtz,[51] Pouchet,[52] and others, act in the same way. "Emphasis must be laid," writes Chittenden,[53] "upon the apparent connection between the thyroid gland and phosphoric acid metabolism," giving as example "the increased excretion of P_2O_5 after feeding thyroids to normal animals, and the great decrease in the case of animals with the thyroids removed."

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[44] Parhon and Golstein: "Sécrétions Internes," pp. 607 and 609, Paris, 1909.
[45] Nothnagel and Rossbach: "Therapeutique," p. 261, 1889.
[46] Gley: La Semaine médicale, May 25, 1898.
[47] Bourcet: Cited by Morat and Doyon: Traité de physiologie, i, p. 470, 1904.
[48] Justus: Virchow's Archiv, Bd. clxxvi, S. 1, 1904.
[49] Henrijean and Corin: Arch. de pharmacodyn., ii, 1896.
[50] Handfield Jones: Cited by Wood: "Therapeutics," 13th ed., p. 409, 1906.

The untoward effects of large doses of thyroid preparations on the nervous system, owing to its wealth in phosphorus and fats, as manifested by tremor, tachycardia, optic neuritis (Coppez[54]), etc., also bespeak a marked influence on this element; Cyon,[55] in fact, found that injections of iodothyrin excited the depressor nerve directly to such a degree that the vascular pressure often declined to two-thirds of the normal.

A familiar action of the thyroid preparations is a rapid reduction of fat in obese subjects when full doses are administered. The presence in the fat-cell of a nucleus rich in phosphorus whose purpose is promptly to promote oxidation of the fat when the organism requires additional carbohydrates explains this action. Schöndorff[56] found that the reserve fats could be exhausted before the nitrogenous tissues were affected.

The mode of action of the thyroid active principle, iodine, is suggested by the presence of this halogen in all nuclei, as shown by Justus[57] and others. This means that iodine is found wherever phosphorus is present, while, as shown above, it is most active where phosphorus is known to be most plentiful. Now, chemistry furnishes, as previously stated, a clue to the manner in which the phenomena I have enumerated occur: "If a fragment of phosphorus lying on a plate is sprinkled with iodine," writes Wilson,[58] "the substances unite, and heat enough is produced to kindle the phosphorus." Nitrogen, hydrogen, and chlorine are ubiquitous constituents of our tissues, and the vigorous explosives they form with phosphorus and the intense liberation of heat the reactions entail are familiar features of the laboratory. Roos[59] found that in a dog in nitrogenous equilibrium iodothyrin "caused at once a marked increase in the output of sodium, sodium chloride, and phosphoric oxide."[60]

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[51] Scholtz: Centralbl. f. inn. Med., Bd. xvi, S. 1041, 1069; 1895.
[52] Pouchet: Bull. gén. de thérap., Sept. 15, 1905.
[53] Chittenden: Trans. Cong. Amer. Phys. and Surgs., iv, p. 93, 1897.
[54] Coppez: Arch. d'Ophthal., Dec., 1900.
[55] Cyon: Arch. de physiol., x, p. 618, 1898.
[56] Schöndorff: Arch. f. d. ges. Physiol., lxiii, S. 423, 1896; lxxii, p. 296, 1897.
[57] Justus: *Loc. cit.*
[58] Wilson: "Inorganic Chemistry," p. 294, 1897.

Finally, as stated in the italicized postulate, "the thyroparathyroid constituent of the hæmoglobin enhances oxidation by increasing, as a ferment, the vulnerability of all cells" to the action of adrenoxidase. That is shown by many facts.

Chantemesse and Marie, Ballet and Enriquez,[61] Bourneville,[62] Shattuck,[63] Lorand,[64] and many other clinicians, including myself, have noted that thyroid preparations caused a rise of temperature of several degrees. These observations are controlled by those of Stüve and Thiele and Nehring,[65] that thyroid extract increases over 20 per cent. the oxygen intake and to nearly as great a degree the carbonic acid output. This is evidently produced by the active agent of the thyroid secretion, iodine, for this halogen itself increases oxidation as well. Thus, Rabuteau, Milanese, and Bouchard,[66] Henrijean and Corin[67] have all noted an increase of nitrogen excretion. Wood[68] and Cushny[69] state, in fact, that iodine can produce fever. Heinrich Stern[69a] noted a rise of temperature at times of 3° F. in cases of hyperthyroidia.

Removal of the thyroid, on the other hand, lowers oxidation. Albertoni and Tizzoni, and Magnus-Levy[70] found, for example, that this procedure decreased markedly the output of carbon dioxide, and that it caused hypothermia. The fall of temperature is gradual, according to Lorrain-Smith,[71] and most marked, according to Rouxeau,[72] at the end of the operation. The proportion of red corpuscles is reduced, according to Moussu.[73] Reverdin observed in man that the hæmoglobin was also diminished, while Horsley noted increased sensitiveness to cold.

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[59] Roos: Münch. med. Woch., No. 47, S. 1157, 1896.
[60] Cited by Chittenden: *Loc. cit.*, p. 98.
[61] Ballet and Enriquez: Cited by Popoff: Arch. gén. de méd., Oct., 1899.
[62] Bourneville: Arch. de neurol., Sept., 1896.
[63] Shattuck: Boston Med. and Surg. Jour., June 30, 1904.
[64] Lorand: Lancet, Nov. 9, 1907.
[65] Thiele and Nehring: Zeit. f. klin. Med., xxx, S. 41, 1896.
[66] Bouchard: C.-r. de la Soc. de Biol., pp. 227, 237, 1872.
[67] Henrijean and Corin: Arch. de pharmacodyn., ii, 1896.
[68] Wood: "Therapeutics," 13th ed., p. 499, 1906.
[69] Cushny: "Pharmacology and Therapeutics," 4th ed., p. 514, 1906.
[69a] Stern: Archives of Diagnosis, July, 1911.
[70] Magnus-Levy: Zeit. f. klin. Med., Bd. xxxiii, S. 269, 1897.
[71] Lorrain-Smith: Jour. of Physiol., vol. xvi, p. 378, 1894.
[72] Rouxeau: Arch. de physiol., vol. xxix, p. 136, 1897.
[73] Moussu: C.-r. de la Soc. de Biol., p. 772, 1893.

Albertoni and Tizzoni and Masoin found that the blood contained less oxygen than normally.

This applies as well to removal of the parathyroids, which was found by Jeandelize[74] also to lower the temperature. That the thyroid apparatus can itself raise the temperature, is shown by the febrile process and sense of heat with flushing observed in the sthenic stage of exophthalmic goiter, *i.e.*, when the thyroid apparatus is still overactive. When thyroid extract is given to such cases, the exchanges may be increased to a surprising degree —77 per cent. in a case observed by Hirschlaff.[75] The disease may in fact be brought on by thyroid preparations, as noted by Notthaft[76] and other clinicians.

Still, as Chittenden states,[77] "according to Baumann, doses of 1 milligramme of iodothyrin, which contain only 0.1 milligramme of iodine, will produce a decided effect upon a goiter after three or four applications, thus clearly indicating that it is not the iodine *per se* that is effective, but rather the iodine compound." This will recall the observations of Notkin and White and Davies that the action of the adrenal secretion resembles that of an organized ferment, and my own that the adrenal principle with which the iodine is combined endows it with the properties of a ferment, the purpose being probably to increase the activity of the iodine on the cellular phosphorus.

THE THYROPARATHYROID SECRETION AS WRIGHT'S OPSONIN.

Fraenkel isolated from the thyroid what he termed a "thyroantitoxin," which he thought served to neutralize in the gland itself toxic substances brought to it by the blood. Notkin also separated a substance he called "thyroproteid," a product of tissue exchanges which he believed reached the organ, to be destroyed therein by a ferment, thyroidin, formed locally. These and all other theories, including Blum's, which restrict the antitoxic process to the gland itself have not stood the test of time. These conceptions are now only of historical interest, many investigators having shown that whatever function the thyroparathyroid apparatus may carry on should be attributed to the passage of its secretion into the blood, in which its active principle, in organic combination, has been found by Gley, Bourget, and others, both in man and the lower animals. The evidence submitted in the foregoing pages fully sustains this position.

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[74] Jeandelize: "Insuffisance thyroidienne et parathyroidienne," p. 45, 1903.
[75] Hirschlaff: Zeit. f. klin. Med., Bd. xxxvi, Nu. 3-4, S. 200, 1898-99.
[76] Notthaft: Centralbl. f. inn. Med., Apr. 9, 1898.
[77] Chittenden: *Loc. cit.*, p. 90.

What the prevailing views are concerning the rôle of the thyroid secretion, and what my own researches represent in respect to them, may be graphically illustrated by quoting the recently published words of Youchetchenko, of the Institute of Experimental Medicine of St. Petersburg.[78] "Some suppose that it [the secretion of the thyroid] is necessary for the development of the bones, the digestion, the nervous system, etc.; others express the opinion that it fills the rôle of antitoxin, which renders non-toxic the toxic products of nutritional exchanges; others, finally, affirm that the toxic substances elaborated in the economy are transformed, under the influence of the ferment in the thyroid, into substances necessary and even indispensable to the life of the organism."

If the function I ascribe to the thyroid apparatus was clearly defined in the foregoing pages, it will be seen that they harmonize all those outlined by Youchetchenko. The labilizing or sensitizing action I attribute to the iodine (in organic combination) on tissue phosphorus explains the action of the thyroid product upon "the development of bones, the digestion, the nervous system," etc., since it is an essential feature of their metabolism —that which renders all tissues susceptible to adequate oxidation, the underlying factor of normal development and function. The "transformation under the influence of the ferment in the thyroid" is naught else than the above process carried out, we have seen, under the influence of a ferment and the organic iodine, *i.e.*, by what I have termed "thyroiodase." As to its rôle as "antitoxin," we shall now see that it is also a feature of the same process.

Youchetchenko attributes to Marbé, Malvoz, Fassin, and Stépanoff (the first- and last- named investigators being of the Pasteur Institute) the credit of having first connected the thyroparathyroid secretion with the modern conception of immunity, which takes into account the presence of alexins, opsonin, etc., in the blood; but this is an oversight which Léopold-Lévi and H. de Rothschild, of Paris, corrected in their recent work[79] when they wrote: "Sajous has attributed to the secretion of the thyroid gland an action which he deems similar to that of the opsonins and to autoantitoxins. More recently, Miss Fassin, M. Stépanoff, M. Marbé have confirmed on their side the influence of the thyroid on the blood's asset in alexins and opsonins. All these researches explain the mechanism of everyday infections."

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[78] Youchetchenko: *Loc. cit.*, Tome xv, Nos. 3 and 4, 1910.

That I am entitled to the priority of this discovery will be shown presently in the course of the evidence in support of my contention, advanced several years ago,[80] that

The thyroparathyroid secretion increases the germicidal and antitoxic power of the blood by endowing the albuminous portion of the hæmoglobin with sensitizing properties. As such, it is the blood constituent Sir A. E. Wright has termed "opsonin."

Bordet's sensitizing substance, or "sensibilisatrice," was thought by this investigator and also by von Dugern to appear in the blood under the influence of the red corpuscles. Nolf[81] showed, however, that it is owing to an action of the alexins or complement upon these cells that "the contents of the latter" are caused *to leave* them; he found also that "the injection of the corpuscular *contents* incites hæmolysis." Now, Savtchenko[82] has pointed out that the "sensibilisatrice" is endowed with specific opsonic properties, acting both on bacteria and leucocytes—the identical sensitizing action discovered by Denys and Leclef[83] in 1895, and which Sir A. E. Wright has since studied with such promising results. Suggestive in this connection is Nolf's statement in reference to the production of antibodies that "it is solely to the injected red corpuscles that the power to bring forth these new substances must be attributed." When this is coupled with Barratt's[84] observation that opsonins "are also produced by injecting red blood-cells in the peritoneal cavity" of experimental animals, and also Briscoe's[85] to the effect that opsonin is present in the fluid of the peritoneal cavity, which normally contains no phagocytes, it becomes evident that opsonin is a product of the red corpuscles.

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[79] Léopold-Lévi and Rothschild: "Physio-pathology of the Thyroid Body," etc., 1911.
[80] Sajous: See vol. i, 1st ed., p. 762, 1903, and vol. ii, p. 1093, 1907.
[81] Nolf: Annales de l'Institut Pasteur, xiv, pp. 297 and 492, 1900.
[82] Savtchenko: *Ibid.*, xvi, p. 106, 1902.
[83] Denys and Leclef: "La Cellule," xi, p. 198, 1895.
[84] Barratt: Proc. Royal Soc. of London, lxxvi, p. 534, 1905.
[85] Briscoe: London Lancet, Sept. 7, 1907.

Under these conditions, however, the administration of thyroid preparations should increase the immunizing properties of the blood, and particularly its opsonic activity. As to the former, I was led to conclude, in 1903,[86] by an analysis of the whole question, that the injection of various bacterial toxins in man and in the lower animals excited more or less actively according to their virulence the pituitary, adrenals, and thyroid (constituting what, as we shall see in another chapter, I termed the "adrenal system"), and that "the various antitoxic sera are more or less active in proportion as to the quantity of thyroiodine in them is great." Four years later, Miss Fassin[87] found not only that removal of the thyroid decreased the germicidal and hæmolytic alexins in the blood, but that the administration of thyroid by any method increased materially these same alexins. That this actually increases the defensive power of the body was also noted by Reid Hunt,[88] who found that when mice were fed on small amounts of thyroid they showed marked resistance to poisoning by acetonitrile. Ever since the gland has been used as a therapeutic agent, in fact, it has been found useful, though empirically, in intoxications of various kinds. Léopold-Lévi and de Rothschild,[89] for example, observed clinically that thyroid treatment rapidly influenced favorably autointoxications and exogenous infections, including erysipelas. Turró[90] found that the juices of swine and sheep thyroids dissolved almost entirely the comma, typhoid, and anthrax bacilli, the bacillus coli communis, and the streptococcus. Conversely, dogs were found by Charrin[91] to succumb readily to infections, after removal of the thyroid. That toxic intermediate wastes or other toxics are not destroyed adequately in thyroidectomized animals is shown by the observation of Gley[92] that the blood-serum of thyroidectomized dogs is more toxic than normal serum, and gives rise to convulsions when injected into animals. Jeandelize and

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[86] Sajous; See vol. 1, 1st ed., p. 763, 1903.
[87] Fassin: C. r. de la Soc. de biol., Mar. 9 and 23 and Apr. 20, 1907.
[88] Hunt: Jour. Amer. Med. Assoc., July 20, 1907.
[89] Léopold-Lévi and de Rothschild: *Loc. cit.*
[90] Turró: C. r. de la Soc. de biol., lx, p. 464, 1908.
[91] Charrin: Les Défenses Naturelles de l'Organisme, Paris, 1898.
[92] Gley: Archives de Physiologie, No. 4, p. 770, 1895.

Perrin[93] also found that thyroidectomized rabbits presented less resistance to poisoning by sodium arsenas than normal animals. Lorand observed the same fact in connection with chloroform narcosis. De Luca and d'Angerio[94] and others have found, moreover, that the urine in thyroidectomized animals contains a greater percentage of toxic substances than normal, and that the therapeutic use of thyroid in these animals counteracted this toxicity. It is thus apparent that the evidence from every phase of the question points to the thyroid secretion as an important factor in the immunizing processes of the body.

The process through which the thyroparathyroid secretion carries on this important function differs in no way from that which enables it to sustain metabolism and nutrition. As stated by Jordan:[95] "The bodies of bacteria contain from about 80 to 88 per cent. of water, the amount showing considerable variation and depending partly on the nature of the organism, partly of the culture-medium. The ash is *largely phosphoric acid*, the P_2O_5 often reaching as high as half the total ash weight (tubercle bacillus, 55.23 per cent.; de Schweinitz and Dorsett[96])." Bacteria, therefore, in keeping with many of our tissue-cells, are relatively rich in phosphorus and correspondingly vulnerable to the action of the thyroiodase. As the latter, in turn, renders the phosphorus prone to oxidation by the plasmatic adrenoxidase, the whole pathogenic micro-organism is rendered unstable chemically and vulnerable to the digestive influence of the blood's germicidal agents—which in the above sense include both the thyroparathyroid and adrenal products acting conjointly.

On the whole, the evidence and the confirmatory testimony submitted under the last two headings have shown:—

1. *The thyroparathyroid secretion and the thyroid preparations used therapeutically act by increasing the sensitiveness of the phosphorus of all cells, particularly their nuclei, to the oxidizing action of the adrenoxidase, and thus enhance metabolism and nutrition.*

2. *They also, in virtue of this action, augment the autoprotective, or immunizing, power of the blood, by increasing the*

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[93] Jeandelize and Perrin: Réunion biol. de Nancy; cited by Parhon and Goldstein, loc. cit., p. 554. 1909.

[94] De Luca and d'Angerio: Revista medica e terapeutica, No. 9, 1896.

[95] Jordan: "General Biology," 2d ed., p. 67, 1910.

[96] De Schweinitz and Dorsett: Centralbl. f. Bakt., Bd. 22, S. 209, 1897.

sensitiveness (as opsonin) of all bacteria, their toxins, endotoxins, toxic wastes, etc., that contain phosphorus to oxidation, and thereby to the digestive or destructive action of the complement, both in the blood and in its phagocytes.

As will be shown elsewhere in this work, this represents the foundation (with the adrenal and pancreatic secretions as additional factors) of the autoprotective process, including the germicidal cytase of phagocytic cells. It traces them to their origin and furnishes their identity, features which Ehrlich's labors have not, so far, determined.

THE PITUITARY BODY AS THE SEAT OF THYROPARATHYROID CENTER.

So important are the functions of the thyroparathyroid apparatus that we cannot but surmise that, in keeping with many other and far less prominent functions, they are regulated by a center. The evidence available, a part of which is given below, and in the second volume, indicates that such is the case.

That it should be the same center which we have seen governs the functions of the adrenals is not only sustained by what evidence there is on the subject, but also by logical reasoning, since the two centers which regulate oxygenation, metabolism, and nutrition, thus conjoined, are placed in the most advantageous position to co-ordinate these all-important functions.

The first clue to such a functional relationship was afforded by the fact that

The active and passive phenomena evoked by the pituitary body and the thyroid apparatus show considerable parallelism.

We have seen that removal of either the pituitary or the thyroid causes a steady decline of the temperature with decreased oxygen intake and carbon dioxide output, and also weakness, tetany, and even epileptic convulsions, while, conversely, overactivity of either organ provokes excessive metabolism with increase of oxygen intake and carbon dioxide output, and glycosuria. We arrest nutrition by removing either the pituitary or the thyroid, just as degenerative changes in either organ entails denutrition lapsing into fatal cachexia. The sthenic stage of acromegaly and gigantism strikingly illustrates the power of the pituitary to incite excessive nutrition and overgrowth; the rapid growth of the cretin under the influence of thyroid preparations exemplifies what the thyroid apparatus can do in the same direction.

The simultaneous presence of degeneration of the pituitary and myxœdema in cases reported by Ponfick,[97] J. Stewart, Codd,[98] Sainton and Rathery,[99] and others; and of acromegaly with exophthalmic goiter by Murray,[100] Lancereaux,[101] and others (two diseases which, as emphasized by Lorand, not only present many characteristics in common, but which, as observed by Magnus-Levy,[102] are attended by excessive oxidation) clearly suggest functional parallelism. This is further emphasized by the enlargement of both organs during pregnancy indicated by the labors of Comte,[103] Launois and Mulon,[104] and Lang[105] and its subsidence when, after parturition, the blood no longer receives the excess of wastes that the presence of the fœtus involved. On the whole, we can certainly say with Thaon[106] that "between the pituitary and the thyroid there is so much analogy that the one cannot be studied without a knowledge of the other."

Zoölogy affords various landmarks in the same direction.

The pituitary body governs oxygenation, metabolism, and nutrition in all animals supplied with a thyroid gland and adrenals.

In tunicata, the homologue of the thyroid, according to zoölogists, is the endostyle, a long gland at the base of the pharynx closely related to the branchial or respiratory chambers. The adrenals in these invertebrates are represented, as personal researches have suggested, by the dorsal tubercle, which is so related to the respiratory chamber that its product, which corresponds with the adrenal secretion, can be secreted into the blood near the oral aperture, the inlet for the water which supplies the animal with oxygen. Suggestive in the light of the views I have submitted is that the dorsal tubercle—the primitive organ of the adrenals from my viewpoint—is connected by a delicate duct with an organ, the subneural gland, which Julin, as we shall see presently, has identified as the hypophysis, while the endostyle, the primitive thyroid, along with all other organs, receives nerve-fibers from a nerve-ganglion attached to this ancestral pituitary.

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[97] Ponfick: Zeit. f. klin. Med., xxxviii, Nos. 1, 2, u. 3, 1900.
[98] Codd: British Medical Journal, May 5, 1896.
[99] Sainton and Rathery: C. r. de la Soc. méd. des hôpitaux, May, 1906.
[100] Murray: Edinburgh Medical Journal, February, 1897.
[101] Lancereaux: La Semaine médicale, June 24, 1896.
[102] Magnus-Levy: British Medical Journal, April 3, 1903.
[103] Comte: Thèse de Lausanne, 1898.
[104] Launois and Mulon: Ann. de gynéc. et d'obstét., 2d series, i, p. 2, 1904.
[105] Lang: Zeit. f. Geburts. u. Gynäk., xl, p. 34, 1899.
[106] Thaon: *Loc. cit.*, p. 116.

Two important facts impose themselves in this connection: The first is that, as stated by Jacques Loeb[107] in reference to a group of these invertebrates, "the central nervous system is reduced to a single ganglion"; the second is that this single ganglion corresponds with the neural or posterior lobe of the pituitary. Just as the nerve-ganglion governs the functions of the primitive thyroid and adrenals, that is to say, the respiratory processes in these lowly animals, so can it be shown to do at every step of the phylogenetic scale up to man, since it preserves its functional importance throughout. The snail, for example, is supplied with both a cerebral and an œsophageal ganglion; galvanic excitation of the cerebral ganglion, as shown by Vulpian, produces no appreciable effect; but similar excitation of the lower or pharyngeal ganglion, the future neural lobe of the pituitary, provokes violent muscular movements. Again, removal of the cerebral ganglion will not kill the animal, but it will remain motionless. Extirpation of the œsophageal ganglion, on the other hand, causes its death in less than twenty-four hours. All this applies as well to other invertebrates.

We can assimilate all the vertebrates to these primitive forms by removing the brain. That the respiratory mechanism or the processes it influences are not in the least impaired by this operation was shown when we traced the governing centers of this mechanism—to which the thyroid belongs—to the pituitary. The well-known Cornell frog lived several years after its brain had been removed. The decerebrated pigeon is a familiar example of this kind. Another is Goltz's dog which lived eighteen months after both its hemispheres had been removed. Conversely, we have seen how rapidly extirpation of the pituitary proves fatal in the higher mammals, just as it does in the low invertebrates when the œsophageal ganglion is extirpated. We found that all the lethal phenomena are due to arrest of respiration and oxidation, both of which processes are carried on through the adrenals and the thyroids. Again,

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[107] Jacques Loeb: "Studies in General Physiology," part 1, p. 363, 1905.

In vertebrates the pituitary body is connected with the thyroparathyroid apparatus, as it is with the adrenals, by direct nerve-paths.

The thyroid apparatus, as all textbooks teach, receives its nerves from the sympathetic through the middle and inferior cervical ganglia. That they originate in the pituitary is shown not only by the presence of typical sympathetic fibers between the pituitary and the upper connections of the spinal system with the cervical sympathetic, but also by the effects of electrical excitation of the exposed, but normal pituitary.

As to the origin of the nerves, Cajal,[108] Joris,[109] and others, we have seen, traced in various animals fibers from the pituitary to a nucleus of large gray cells immediately above the infundibulum in the anterior portion of the third ventricle, which nucleus was found by them to project nerves over the ventricular walls. These nerves are also described by Edinger[110] in fishes, reptiles, and birds as "numerous fine, medullated fibers"—the characteristics of sympathetic nerves, as shown by Bidder and Volkmann. In illustrations of sections in various animals, Edinger shows, moreover, that several bundles of these fibers project posteriorly as far as the level of the bulb, whence, as is well known, the fibers which pass over to the sympathetic ganglia begin to leave the spinal system. As the ganglia are the starting points of sympathetic nerves to the various organs, we thus have, through these ganglia, a continuous path from the pituitary to these organs. This is sustained by physiology, since Cyon and also Masay[111] caused an instantaneous rise of pressure of over 100 mm. Hg. by exciting electrically the exposed pituitary. As the vagi were cut during the experiment, and the vasomotor center is independent and located in the bulb, the rise of pressure could only be due to general sympathetic vasoconstriction. I will show in the second volume that the pituitary has a controlling power over the sympathetic system.

When the influence of the pituitary over the adrenals was analyzed, it was possible to trace step by step along the path between the two organs all the main phenomena which both were able to provoke. In the case of the thyroid we are deprived of this valuable testimony. As Morat,[112] in his review of the sympathetic system, says, "the thyroid gland receives its vasomotor fibers from the superior portion of the thoracic chain by the cervical cord. Stimulation of the thoracic chain causes either vasoconstriction or vasodilatation on account of the mixture of the two orders of fibers." In other words, the antagonistic nerves which control the functions of the thyroid are so conjoined that transection or excitation would afford no reliable testimony.

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[108] Cajal: *Loc. cit.*

[109] Joris: *Loc. cit.*

[110] Edinger: "Anatomy of the Central Nervous System," American edition, p. 209, 1899.

[111] Masay: Ann. de la Soc. roy. des sci. méd. et nat. de Bruxelles, xii, part iii, 1903.

The participation of the thyroid in the phenomena awakened by the pituitary and the nerves it projects posteriorly is shown, however, by the intensity of these phenomena. The adrenal secretion alone, as represented by its extracts, causes a rise of temperature of 1° or 2° F. How account for the rise of 10° F. and over caused by puncture of the tuber cinereum (just above the pituitary) by Sakowitsch[113]; of the 6° F. and over noted by Brück and Günther[114] on puncturing between the pons and medulla, and of the 12.4° F. noted by Brodie[115] after an injury of the cervical portion of the spinal cord, with impulses to the adrenals alone to account for these heat phenomena? They obviously fail to do so. On the other hand, they are readily explained by *simultaneous* impulses to the thyroid apparatus, since the action of its secretion upon cellular phosphorus, we have seen, provides an active source of heat energy. This dual action not only accounts for the high temperatures obtained by irritation applied all along the path from the pituitary down to where the nerves to the adrenals and thyroid leave the spinal cord, but it indicates that the two sets of thermogenic nerves follow the same path, down to this region.

Finally, that the pituitary is so related with the nervous system as to be capable of governing these organs, is further shown by the fact that, as stated by Prof. Laulanié,[116] a physiologist who has given considerable attention to the functions of the ductless glands, in reference to the pituitary body, "this gland is, in fact, in relation with the sympathetic, the vagus, and the depressor nerve."

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[112] Morat: "Physiology of the Nervous System," Syers's ed., p. 224, 1906.
[113] Sakowitsch: *Loc. cit.*
[114] Brück and Günther: *Loc. cit.*
[115] Brodie, Morat, and Doyon: *Loc. cit.*, Article Calorification, p. 412, 1899.
[116] Laulanié: "Éléments de Physiologie," 2d ed., p. 488, 1905.

Of course, I am familiar with the prevailing view that the pituitary is a secreting gland. But the data which tend to sustain this opinion are far from convincing, for reasons that I will submit in the tenth chapter. Suggestive in this connection is the fact that its removal for tumors or other lesions which destroy its functions does not in the least compromise life, as is the case after removal of the adrenals or of the thyroparathyroid, which are known to be secreting glands. Were the pituitary the source of any such secretion, its extirpation would obviously provoke serious disturbances. With this organ interpreted in accord with my views, *i.e.*, as a co-ordinating center acting through subsidiary centers in the bulb capable of assuming its functions increasingly as these are being annulled by the pituitary lesion, absence of postoperative complications is explained.

Again, the main evidence of those who believe in the existence of an internal secretion is based on the rise of the blood-pressure observed after injections of pituitary extract. "According to Kohn,"[173] writes Swale Vincent in his recent work,[174] "there is nothing to suggest that the posterior lobe has an internal secretion, in spite of all the results of experiments involving the injection of extracts." . . . "We have seen that the extracts having powerful effect upon the blood-pressure and the flow of urine are obtained from the posterior lobe and not from the epithelial layer which covers it. This view seems to be borne out by the experiments of Franchini. Now, the posterior lobe proper (excluding the epithelial layer) consists of neuroglia, pigment, and occasional nerve-cells." Swale Vincent then aptly remarks: "It is extremely difficult to imagine how such a structure can be regarded as a secreting gland."

Pending additional evidence to this effect, to be submitted later on, and also for testimony concerning the connection between the pituitary and the adrenals, the conclusion is submitted that

The pituitary body contains the governing center of the thyroparathyroid apparatus and adrenals, and co-ordinates the secretory activity of these organs.

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[173] Kohn: Münch. med. Woch., Nu. 28, 1910.
[174] Swale Vincent: "Internal Secretion and the Ductless Glands," p. 401, 1912.

CHAPTER IV.

DISEASES OF THE THYROPARATHYROID APPARATUS.

DISORDERS DUE TO DEFICIENT ACTIVITY OF THE THYROPARATHYROID APPARATUS.

In the light of the data and conclusions submitted in the preceding chapter, the phenomena awakened by functional disorders of any kind in the parathyroid apparatus should be of two kinds: those due to excessive functional activity now known as "hyperthyroidism," and those due to inadequate functional activity, and designated as "hypothyroidism." A third class, termed by Léopold-Lévi and Rothschild "thyroid instability," introduces both the former types, but either in alternation or concomitantly in the same subject. In the present chapter we shall consider the first type, viz., that in which, as stated in the above heading, the functions of the thyroparathyroid apparatus are inadequate, in that the secretion it supplies the organism is insufficient to carry on normally the functions described in the foregoing pages.

The classification of the disorders due to deficient activity of the thyroid apparatus being in its formative stage, so to say, many expressions and terms have been introduced, such as "thyroid insufficiency" or "inadequacy"; "hypothyroidism," or "attenuated," "benign," "incomplete myxœdema"; "myxœdeme fruste," and others, to denote the milder forms of this disorder; and quite as many others to designate the severe forms considered in the next chapter. None of these terms seem to me to interpret satisfactorily the morbid process in question. Restricting ourselves for the moment to the milder forms, such terms as "thyroid insufficiency" or "inadequacy" are too cumbersome; "hypothyroidism" implies the presence of a habit such as "alcoholism"; "incomplete myxœdema" and "myxœdeme fruste" are not applicable in most instances of this disorder, since no myxœdema of the skin, mucous membranes, etc., is discernible.

Worst of all is the term "athyrea," which perverts the name of the gland, "thyro-" or "thyroid" being necessary in composition to indicate a connection with the "shield-like cartilage." It has appeared to me, therefore, that the simplest term would fill our needs best, until the many morbid states and syndromes it covers will have been, to say the least, more accurately identified. Of all the terms available is that adapted from the French "hypothyroidie," *i.e.*, *hypothyroidia*, which also presents the advantage of corresponding as to its terminal with anemia, hyperchlorhydria, and many other terms in current use.

As to the pathogenesis of this condition, it must also be said that at the present time little or no effort is made by writers to explain the manner in which thyroid insufficiency brings about each of its characteristic symptoms. The functions I have attributed to the thyroid and to the adrenals in the preceding chapters enable us to do otherwise. In the present connection, therefore, it is essential to recall that, with these functions in abeyance or depressed, we shall have to deal with three essential morbid factors:—

1. Deficient tissue oxidation, the rate of metabolism and nutrition in all tissues, particularly those rich in phosphorus, such as the nervous system, cellular nuclei, etc., being retarded.

2. Deficient breaking down of waste products, fats, etc. (slowed metabolism entailing deficient catabolism), with accumulation of fat, detritus, wastes, etc., in the blood and tissues as a result.

3. Deficient resistance of the body to infection and intoxication, owing to insufficient production of opsonin (the thyroparathyroid secretion) and of the other antitoxic and germicidal blood constituents and phagocytic cells, as a result of the slowed metabolism in all organs producing them.

HYPOTHYROIDIA.

(Chronic Benign Hypothyroidia; Hypothyroidism; Incomplete Myxœdema; Myxœdème Fruste.)

The term "hypothyroidia" is intended to include all conditions of the organism that are due to deficiency of the thyroparathyroid secretion, but not the advanced types of this condition, such as myxœdema and cretinism, which are reviewed farther on. It includes the so-called "incomplete" form, and, as such, is far more important clinically than even myxœdema, since, as we shall see, it forms part of, or complicates pathogenically, many diseases that we meet almost daily in practice.

The history of hypothyroidia is linked with that of its more severe form, myxœdema. The results of surgical removal of the thyroid by the brothers Reverdin were reviewed early in the preceding chapter. The medical side of the question, as regards the milder form with which we are now concerned, was first described by J. L. Reverdin,[1] one of the two brothers referred to above, in 1887, who gave it the name of *myxœdème fruste.* Valuable articles on the subject were then contributed by Thibierge,[2] Chantemesse and Marie,[3] Murray[4] and Brissaud,[5] and others, in which many cases were reported, but that of Hertoghe,[6] of Antwerp, in which he termed the disorder "chronic benign hypothyroidia" is worthy of special attention owing to the multiplicity of clinical features introduced and the accuracy of the author's conclusions.

While many symptoms of hypothyroidia are witnessed in myxœdema, the latter in its typical form is a comparatively rare disease. The former is also thought to be infrequent, but this is merely because it generally passes unrecognized. This is mainly due to its classic association with the frank type of myxœdema, which leads the clinician to seek for the most salient symptoms, *e.g.,* cutaneous myxœdema, dry skin, the mask-like face, etc. Not finding these phenomena he transfers his analysis of the case to other possible morbid processes. In truth, the symptom-complex of hypothyroidia does not, in the great majority of cases, include the prominent symptoms of myxœdema. Moreover, while the latter disease is progressive when left untreated by modern methods, hypothyroidia is not; but it keeps the patient in a state of perpetual torment. The physician, failing to recognize the true identity of the trouble, leaves the patient a prey to acute suffering from so-called rheumatism, neuralgia, tic douloureux, sciatica, etc. The sufferer finally abandons treatment—at least that offered by medical men.

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[1] Reverdin: Revue méd. de la Suisse Romande, vol. vii, p. 275, 1887.

[2] Thibierge: Gazette des hôpitaux, vol. lxiv, p. 117, 1891.

[3] Chantemesse and Marie: Bull. et mém. de la Soc. méd. des hôpitaux de Paris, vol. xi, p. 124, 1894.

[4] Murray: British Medical Journal, Oct. 1, 1898.

[5] Brissaud: "Nouv. iconographie de la Salpêtrière," p. 240, 1897.

[6] Hertoghe: *Ibid.*, p. 261, 1899.

Another perhaps still broader field in which the recognition of hypothyroidia is of great practical importance is the process of development, physical and mental, of the child. We have sufficient evidence of the effects of athyroidia (complete deficiency of normal thyroparathyroid secretion) in cretinism, *i.e.*, infantile myxœdema. That a reduction of the same secretion should compromise correspondingly the physical and mental welfare of a child without necessarily branding it with the physical signs of cretinism is an established, though little recognized, fact. Indeed, a large proportion of backward children and the oft-punished laggards of the class-room are but sufferers of hypothyroidia.

Finally, certain diseases, syphilis, tuberculosis, and other infections, and also certain abuses of the physical powers, such as multiple pregnancies, prolonged lactation, excessive venery, or masturbation, so weaken the thyroparathyroid apparatus and the adrenals, with which it is, we have seen, intimately linked functionally, that hypothyroidia results. The recognition of this condition as an underlying factor means not only a marked development of our diagnostic resources, but it affords also opportunities for successful therapeusis where, before, failure was the rule.

A definition which appears to me to facilitate the recognition of this disease is the following:—

Hypothyroidia is a constitutional disease due to deficient functional activity of the thyroparathyroid apparatus, when the secretory activity of the latter is not sufficiently impaired to give rise to the most advanced and progressive type of the disease: myxœdema. The symptoms of hypothyroidia most frequently met with, separately or unitedly, are: severe occipital and interscapular pain, obesity with supraclavicular fat pads, hypothermia, loss of hair and teeth, lassitude, stubborn constipation, and mental torpor, supplemented in children by slow physical, mental, and irregular skeletal development, enlargement of the lymphatic glands, and, occasionally, enuresis.

SYMPTOMATOLOGY.—The symptomatology of hypothyroidia includes many of the symptoms of the asthenic disorders of nutrition, but, as there exist many gradations of this condition, hypothyroidia representing as many degrees of thyroparathyroid secretory activity, its symptoms are more or less prominent both in number and intensity.

These patients usually apply for relief of pain of some kind, particularly pain in the back or in the occipital region, and occasionally for migraine or neuralgia. The "backache" may consist of sacrolumbar pains, of coccygodynia, or in most instances of very severe deep-seated pain between the shoulder-blades, which rest in bed tends to aggravate rather than to improve. These phenomena are due to deficient catabolic activity, the blood being laden with toxic products—a known cause of such symptoms. That rest in bed should aggravate the condition is self-evident: it merely slows still more the oxidation process and thereby encourages the catabolic torpor. They complain of feeling fatigued, languid, somnolent on rising, and of being in every way worse; while, as the day wears on, their condition improves. Their temperature is low, and they complain of always feeling cold, especially at the extremities. Their hands are flabby, damp, though cold chills may even be complained of. We have here an evidence of the slow metabolic activity referred to above, every sign of deficient oxidation being present. This explains also why a copious meal, especially if it includes the use of alcoholic beverages, should be a source of great relief in these cases, and why, also, they readily become addicted to the immoderate use of alcohol as a "stimulant."

A close examination then reveals other morbid phenomena which are obviously due to the defective nutrition of all tissues which hypothyroidia entails. The patient appears much older than her age—women constituting a large proportion of these cases. The hair may be prematurely gray, showing a marked tendency to fall in patches from the forehead and median line, which tends to become wider, and from the occiput. This loss, which is attributed by the patient to the headaches, may be such as eventually to cause complete alopecia. In marked cases the hair may be coarse, dry, and brittle, as in the cretin. The eyebrows also show a tendency to fall, but, a characteristic sign of hypothyroidia: the loss is limited to the external or outer ends. This shortening of the eyebrows and the occipital loss of hair denote, jointly, rather marked cases, though the shortened eyebrows are frequently met in the less severe. In the former, the skin of the face may also appear infiltrated and be hard to the touch, as in myxœdema, its color being waxy, with perhaps a reddish patch below each cheek-bone. Although the skin of the body may be normal, that of the legs, especially below the knees, usually feels rough, rasp-like, and may be scaly, the scales, which are readily detached, recalling dandruff, which is also present in most cases. Pads of fat especially prominent over the clavicle seem characteristic of rather marked cases. Such symptoms, which belong to true myxœdema, are rarely observed, however, though a waxy hue of the facial skin and puffy lids are not uncommon.

Dyspnœa or oppression, due to deficient oxygenation of the blood, is complained of on climbing stairs or during continued speaking. Palpitations, sometimes of a distressing character and with severe pain, may also occur. The heart is often found dilated with weak systole and occasional murmurs. The blood-pressure is low, from 80 to 110 mm. Hg., and the pulse weak and rapid. All these symptoms are directly traceable to the existing impairment of the oxidation and nutrition, the cardiac and vascular muscles suffering from this condition as well as all other organs. The blood-forming organs being also inadequately nourished, anæmia is the rule, the erythrocytes being usually reduced to about 3,000,000, with more or less anisocytosis. Every type of cellular alteration seems to have been observed in this disorder, but, as a rule, what changes occur are not very marked. The hæmoglobin may be considerably reduced.

The teeth, especially the molars, tend to become loose and carious unduly early, owing to the deficient calcium and phosphorus metabolism which deficient thyroparathyroid secretion entails, and need the constant attention of the dentist, who, as a rule, informs them that they are gouty—with "uric acid" as main cause of the dental trouble—not a misleading statement so far as the "gouty diathesis" is concerned, for it is closely linked also with hypothyroidia. The teeth are also exceedingly prone to become tartrous and require frequent cleansing. Where the teeth are neglected, as in the poor, they are rapidly lost, frequent toothache causing them to be drawn. The gums tend to bleed readily when brushed and to recede from the teeth, and are red and swollen unless the toilet of the mouth be carefully attended to.

The deficiency of germicidal activity (phagocytic and humoral) manifesting itself where protection is usually quite active, *i.e.*, along mucous surfaces, the nasopharyngeal mucous membrane is also apt to be congested through the local accumulation of germs, the tonsils showing, for the same reason, a predilection to acute inflammation. The nasal mucosa is often found turgescent, owing to passive congestion of the underlying tissues. This gives the voice the nasal "twang," but it may also be husky or otherwise modified or veiled, through infiltration of the laryngeal mucosa. The singing voice tends to be false from the same cause, especially during the menstrual period. A "crick" in the larynx is commonly complained of.

Deficient metabolism and nutrition account for the general asthenia with lassitude and weakness of the knees, which is present in practically all cases. Fibrillary motions of the muscles and trembling occur in severe cases from the same cause. Constipation due to deficient peristalsis is also the rule, and it is often sufficiently obstinate to demand constant purgation—which tends to increase the intestinal torpor. Fecal impaction is not uncommon. The liver is passively congested and enlarged —a fact due to the low general vascular tension which explains also the presence of varicose veins, varicocele, and kindred vascular disorders frequently observed in these cases. They seem also to suffer frequently from biliary or renal calculi, a condition due mainly to deficient germicidal activity of the blood. The urine is often high-colored and scanty, and occasionally contains albumin, casts, sugar, or blood.

Flat-foot is sometimes observed, a condition due to relaxation of the interosseous muscular and ligamentous supports; fœtid hyperidrosis is also marked in some cases. The osseous framework is often defective, "pigeon-breasts," narrow chests, and a predisposition to caries being common.

The organs of generation are often the seat of functional disorders. The uterus is often found retroflexed. Impotence or loss of sexual desire is common. Amenorrhœa is common, but metrorrhagia may also occur, owing to the low vascular tone, particularly of the arterioles. In one of my cases, a girl of 16 years, there was what the parents termed "a constant leak," *i.e.*, a slight, but continuous menorrhagia. In the male, spermatorrhœa and prostatic hypertrophy are often witnessed. Menstruation sometimes fails to appear, especially in congenital cases, owing to inadequate development. The menstrual period is attended by severe lumbosacral pains. Pregnancy often affords considerable relief of all symptoms, owing to the fact that the activity of the thyroparathyroid apparatus is greatly enhanced, though it may be attended by hæmorrhages. Parturition is likewise accompanied by copious hæmorrhages in a larger proportion of cases; such parturients are exposed also to eclampsia, owing to imperfect catabolism of toxic wastes.

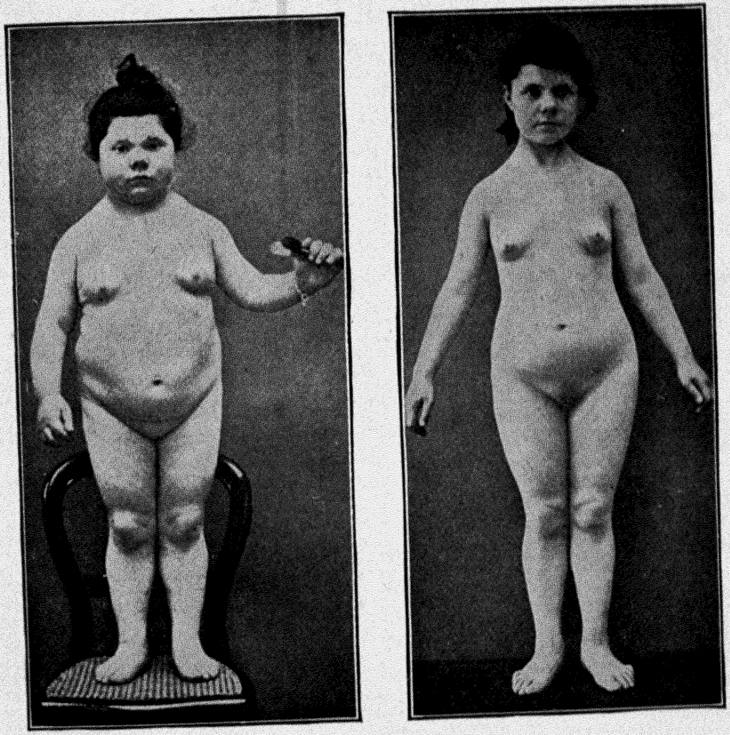
Lactation may act in different ways. The pallor tends to increase in some, and œdema, especially of the ankles, anæmia, lassitude, and intellectual torpor may intervene and last until the infant is weaned. As milk is mainly composed of blood-plasma containing adrenoxidase (as shown by the guaiac and other tests), lactation imposes increased activity upon the adrenals. These organs being weakened by the hypothyroidia, we have seen, all the above hæmorrhagic phenomena occur. In other cases there is marked improvement during the whole period, and the symptoms of hypothyroidia return only after the secretion of milk ceases. In occasional cases, the improvement is permanent.

Hallucinations of sight—as of small animals running across the room—and hearing, rumbling noises or running water, and various forms of tinnitus may occur. These are due to the same loss of vascular tone, and imperfect circulation in the sensory organs.

Melancholia or, at least, an uncontrollable sadness, due to deficient nutrition of the cerebrum, is often witnessed in severe cases, especially during menopause. Maniacal excitement is occasionally observed, owing probably to accumulation of toxic wastes in the blood. The mind, even in the milder cases, is usually obtuse, in the sense that they lack *esprit*, *i.e.*, the ability to grasp the finer points of an argument or of a question treated in the abstract, but they are not in any way comparable to true myxœdematous subjects in this particular, some of whom apoach closely the mental status of cretins. Like the latter, wever, even average cases may have the arched brow and rinkled forehead, the expressionless and sorrowful face, though all intents and purposes of average commonplace intelligence. most instances, however, none of these purely myxœdematous atures can be discerned and a high grade of intelligence even ist, as in one of my cases, whose family—including a high-ade imbecile brother—and descendants show distinct traces of pothyroidia.

The thyroid affords very little information under physical amination in these cases. One lobe may feel smaller than the ther when, on the patient being asked to swallow, the organ is aised under the palpating fingers; the organ may seem unusually mall, and the neck unusually flat; but again, it may appear nlarged. On the whole, the organic changes are not such in hese cases as to alter sufficiently the outline of the organ to urnish any serious diagnostic aid.

Most authors refer to the disease as one of middle life, but his is an error. This type of hypothyroidia occurs frequently, we have seen, among children, and represents a large proportion of those termed "backward" in the schools, and among those ccused of being "lazy," "slow," and "dull." This applies as well to adolescence, particularly, as in children, in those who are abnormally stout. All these cases may not present the syndrome just described; it is, in fact, rarely met with in any one case, but the superfluous fat, the mental torpor, the slow development, and the carious teeth are sufficient to indicate that the oxidations and metabolism are inadequate. The familiar influence of thyroid preparations on adiposis also points to hypothyroidia as the underlying cause of this condition. It may also assert its presence through a few phenomena of another order in a bright child, to-wit: irregular bony growth, a slight scoliosis perhaps, or true rachitis, flat feet, a narrow thorax, some pallor, hypothermia, undue vulnerability to infection, or one or more of the many other symptoms described above. Some, on reaching the fourth or fifth decade—particularly women approaching or undergoing the menopause—begin to show typical symptoms and soon lapse into full-fledged cases—recalling that several of the symptoms now revealed as part of complete syndrome, sensitive-



HYPOTHYROIDIA. [*Léopold-Lévi and de Rothschild.*]

Physical development under thyroid treatment.

ness to cold, neuralgia, anemia, menorrhagia, etc., had been present many years.

ETIOLOGY AND PATHOLOGY.—The causes of hypothyroidia may be divided into two classes, the hereditary and acquired.

The most important *hereditary* causes which entail defective development, morphological and secretory, are syphilis, alcoholism and the gouty diathesis. Even far back in the parental lines on either side, these transmit their influence through the intermediary of the ductless glands, especially the thyroid, adrenals, and pituitary body, which, jointly, in the light of the data submitted, carry on oxidation and metabolism and thus constitute, so to say, the tripod of the vital process. The maternal line is generally thought to transmit hypothyroidia in the majority of instances. It happens that some of the most marked cases I have had were clearly traceable only through the paternal ancestry—three generations in one instance. Consanguinity in marriage probably owes its evil effects to the presence in the family of one of the deteriorating diseases mentioned. Conversely, marriage of a girl suffering from a mild type of functional hypothyroidia sometimes brings on recovery if pregnancy occurs, the increased activity of the thyroid apparatus this entails causing it to develop its functional powers to the maximum needs of the subject. That the adrenals are also overactive under these conditions—thus sustaining from another direction my view that the adrenals are stimulated by, and concomitantly with, the thyroid—was recently emphasized by the observation of Neu,[7] who found an excess of the adrenal product in the blood throughout the entire period of gestation.

The *acquired* form is often due to the identical factor just referred to as a curative one in some instances. The repetition of pregnancy too many times may not only cause recurrence of hypothyroidia by exhausting the thyroid apparatus, but it may likewise do so in a woman previously free of any disorder of the ductless glands. Prolonged lactation acts in a similar way, the maternal milk serving, we have seen, to protect the nursling against infection. Infectious diseases, especially those of childhood, including the milder ones, measles and mumps, and likewise variola and typhoid, may also produce hypothyroidia by causing interstitial and parenchymatous lesions which lead to sclerosis and atrophy. The resulting phenomena are proportionate, of course, with the degree to which the functions of the thyroid are inhibited. These may occur in the midst of the disease, the child failing thereafter to grow physically and mentally at the normal rate and becoming flabby and pale, and showing the typical symptoms of functional hypothyroidia—if not its more advanced stage, cretinoid infantilism. Traumatism of the thyroid may also produce it. Amenorrhea, as noted by Macfarlane[7a] may be the salient symptom of the disorder.

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[7] Neu: Medizinische Klinik, Nov. 3, 1910.

Old age stands apart perhaps from these two classes in that it is normal to all living things; but the thyroid apparatus stands pre-eminently, we have seen, as the underlying factor in this connection, according to Lorand,[8] who traces the cause of senility back to the thyroid, Victor Horsley, Hale White,[9] Erdheim, and others having found this organ atrophied, and containing connective tissue, in aged subjects. This was found to occur as early as the fiftieth year in the seventy thyroids examined by White. As noted by Erdheim, the same evidences of degeneration appear in the parathyroids. I look upon concomitant changes in all the organs of the adrenal system, the thyroid, adrenals, and pituitary, as the underlying cause of senility.

The symptomatology of senility and that of atrophy of the thyroid gland present considerable resemblance, as Léopold-Lévi[10] holds to hypothyroidia; the wrinkled, dry skin, the subnormal temperature, the alopecia, the thinning of the eyebrows, the loss of teeth, the anorexia and constipation, the diurnal somnolence, the suppression of the menses and of the sexual function, the vague muscular pains, the enfeeblement of all functions, and the tendency to degeneration, particularly of the vessels, being common to both conditions.

TREATMENT.—Small doses of thyroid cause gradual disappearance of the morbid phenomena, while large doses may aggravate them. As emphasized by Hertoghe, the actual secretory activity of the thyroid apparatus is an unknown quantity, and large doses, by suddenly bringing on headache, pain over the kidneys, articular, muscular, and hepatic pains and anorexia—to which I would add a rapid pulse, fever, a tendency to faint, tremors, and increase of the existing dyspnœa—merely serve to frighten the patient and cause unjustified condemnation of the treatment. The treatment should be persisted in for years if need be, as emphasized by a case reported by G. E. Price.[10a]

[7a] Macfarlane: Jour. of the Am. Med. Assoc., Feb. 3, 1912.
[8] Lorand: "Old Age Deferred," p. 91, 1910.
[9] White: Med. Chirur. Trans., vol. lxxi, p. 182.
[10] Léopold-Lévi: Jour. de méd. de Paris, No. 26, 1909.

One grain of the desiccated thyroid gland during meals is sufficient to begin with in an adult. This may be gradually increased until 2-grain (0.132 Gm.) doses are given. Patients seldom stand larger doses well, and these are only warranted when the prolonged use of the smaller fails to improve the patient. Often when improvement is not noticed the fault lies with the preparation administered; a change should then be made. In mild cases one-half of the above doses often suffice.

When the anæmia is profound, the effects of treatment are enhanced by giving desiccated adrenal gland, 2 grains (0.132 Gm.), and a small dose of iron, 1 grain (0.066 Gm.) of Blaud's pill, with each dose of thyroid. Such a small dose of iron does not increase constipation, and contributes to the rapid building up of the hæmoglobin molecule. The three agents can be given in a capsule. The constipation should receive careful attention. High injections of saline solution two or three times a week are sometimes necessary in severe cases to evacuate completely the lower bowel. This measure may be resorted to the first three or four weeks if needed, and replaced by glycerin suppositories until a free motion occurs daily. Usually the fourth week of thyroid treatment is attended by considerable progress in this and all other directions. Saline aperients are to be preferred if purgation *per ora* becomes necessary. Opiates are harmful.

MYXŒDEMA, OR PROGRESSIVE HYPOTHYROIDIA.

In this disease we have the maximum expression of progressive hypothyroidia, as it develops after the process of body growth has been accomplished, *i.e.*, in the adult. When the corresponding disorder occurs during childhood or adolescence, it stunts growth of body and mind and is then known as cretinism, treated under the next heading.

[10a] G. E. Price: American Medicine, Aug., 1911.

The marked inhibition of the thyroparathyroid functions that characterizes this disease is graphically illustrated in its symptomatology when these functions are interpreted from my viewpoint. The great diminution of the thyroparathyroid secretion correspondingly impairs the sensibility of all phosphorus-laden structures, particularly the nuclei of all cells, the nervous system, and the adrenals, to the oxidase of the blood. There results, therefore, general retardation of metabolism, particularly its catabolic phase; this is well exemplified by the hypothermal phenomena, the general functional torpor, the accumulation of fat, and the extravasation of fluids which constitute the cutaneous œdema, the latter being due mainly to passive relaxation of the peripheral blood-vessels. Wastes, detritus, etc., accumulate in the blood also as a result of defective catabolism, giving rise to "rheumatic" and cutaneous disorders. The dystrophies of various kinds with a marked tendency to degenerative processes invariably witnessed in this disorder are also normal results of defective metabolism. Considered in this light the disease may be defined as follows:—

Myxœdema is a functional disease due to marked or complete hypothyroidia when the latter occurs after puberty. It is characterized by deficient oxidation and catabolism, the main symptoms of which are hypothermia, infiltration, and swelling of the cutaneous tissues, including those of the face, increase in weight, dryness of the skin, marked weakness, and mental torpor.

SYMPTOMATOLOGY AND PATHOGENESIS.—The deficient oxygenation is well exemplified by the correspondingly depressed heat production. These patients suffer almost continuously from cold; their temperature, both oral and rectal, being always subnormal—as low as 93° F. in some instances—unless some fever be present. In a case observed by Hun and Prudden, the temperature fell steadily until it reached 66° F., before death. The least exposure to cold causes the lips, nose, ears, and finger-tips to become cyanotic; hence the abundance of covering with which these cases are found provided. The extremities are, as a rule, cold and often purple or livid. This is partly due, however, to the cardio-vascular weakness referred to below.

The deficient metabolism and functional activity is well exemplified by its influence on the cardio-vascular system, the functional torpor of which (partly due to similar condition of the vaso-motor system) gives rise to the pre-eminent symptom of the disease: the peculiar œdema of the skin and mucous membranes. This phenomenon, which led Ord to designate it "myxœdema," is a "jelly-like swelling," as he termed it, which causes the body, particularly the face and suprascapular regions —commonly the seat of cushions or pads—to become irregularly swollen. The infiltrated tissues are elastic, firm, and resistant, but do not pit on pressure, as in true œdema, though they vibrate under lateral stroking. At first the swelling may disappear temporarily or change situation, but after a time it becomes permanent. The abdominal walls being likewise affected, the abdomen appears enlarged and pendulous, with more or less projection of the umbilicus, and sometimes ascites. The genitalia are similarly tumefied as a rule. The hands are also thickened and sometimes spade-like; the nails are brittle and thin, sometimes abnormally curved and ridged, and occasionally undergo atrophy. A similar condition may affect the toes. The forearms, legs, and feet are also the seat of swellings.

The skin, its glandular elements and the hair, all show clearly the effects of defective trophic conditions. The skin, mainly owing to the arrest of its sebaceous and sweat glands, is dry, rough, and scaly, though that of the face may be relatively smooth. It may desquamate in flakes or in the form of a fine powder. Patches of pigmentation varying from yellowish brown to the actual bronzing of Addison's disease (thus affording additional proof of the participation of the adrenals in the functional torpor) are occasionally witnessed.

The hair also changes in appearance; it becomes coarse, lusterless, and breaks easily. It is gradually lost, falling out in patches, at first where the traction attending the use of the comb is greatest, *i.e.*, where the hair is parted, the brow, and the occiput. The lashes and eyebrows are also lost in part, along with the hair of the rest of the body.

As a result of the cutaneous thickening and infiltration, the face becomes coarse, expressionless, and mask-like. The lips, greatly thickened, are usually cyanosed and cause the mouth to appear greatly enlarged. The color of the skin is yellowish or wax-like, a circumscribed patch of redness being present, as a rule, below each cheek-bone. The nose is cold, the tip being sometimes cyanosed; it appears broad and flat through thickening of the nostrils. The ears, being in a similar condition, are likewise enlarged; the auditory meatus, however, is narrowed by its thickened walls, causing more or less deafness. The lids droop over the eyeballs—though exophthalmus may occur, due to primary exophthalmic goiter—causing the patient to appear sleepy, while an effort to raise the upper lid is manifested by elevation of the eyeballs. There is usually considerable lachrymation, due to glandular leakage.

The mucous membranes being involved, as is the skin, those of the mouth and naso-pharyngeal cavities appear pale and tumefied. That of the cheeks is indented by the teeth, against which it presses, and is sometimes bitten; this applies also to the tongue. The teeth tend to decay, and may become black within a comparatively short period, owing mainly to deficient calcium metabolism, or readily break off and fall out. This is greatly aggravated by the recession of the gums and the readiness with which these structures tend to ulcerate and bleed. Stubborn stomatitis, with free salivation, dribbling from the corners of the mouth, and erosions of the buccal, pharyngeal, and laryngo-tracheal membrane, may appear. Œdema of the larynx is not infrequently a cause of death. In some cases, however, the whole oral cavity is uncomfortably dry. The entire alimentary canal, down to the rectum, is also more or less infiltrated, causing anorexia, gastro-intestinal disorders, and constipation, which may alternate with attacks of diarrhœa. There is, as a rule, a profound distaste for meat, which in fact is toxic in a measure to these cases—as it is in thyroidectomized animals—owing to their impaired antitoxic functions.

The tumefaction of the oral mucous membrane and of the palate, tongue, and lips renders enunciation very imperfect and jerky; this condition being aggravated by the narrowing of the naso-pharyngeal lumen, it gives what voice there is a "nasal" character. It is also rendered coarse and low, that of a woman being sometimes lowered sufficiently in pitch to recall that of a man. Approximation of the cords being rendered difficult by the tumefaction, speaking sometimes requires considerable effort. The slow intellection from which these cases suffer—owing to difficult metabolism of the organ of mind—increases greatly the trouble they experience in understanding questions and expressing their wants and ideas, a fact which often renders them extremely irritable. Mental disorders are frequent in these cases. Total lack of interest in their surroundings, somnolence, and amnesia are commonly observed.

The deficient oxidation of all muscular elements entails a corresponding weakness. Great lassitude with exhaustion upon the slightest exertion is the rule. Some cases are unable to raise the head at all or to stand. Others lapse into paralysis. Fibrillary tremor and muscular quivering are often noticed. Locomotion is tentative, often waddling; missteps are frequent, being produced by a slight obstacle. The ataxic gait may prevail; the motions of the arm are also uncertain and unsteady in sufficiently advanced cases. Although the parathyroids have been found sclerosed along with the thyroid in these cases, tetany is very rarely observed- -a fact which further suggests the functional unity of these organs.

Sensation being, as a rule, markedly impaired, while the finger-joints are stiffened, the usefulness of the hands is greatly compromised. Small objects are held with considerable difficulty, and easily dropped, while such diminutive articles as pins, needles, and even small buttons are not felt at all. Tingling, formication, and pruritus are often complained of. Although cutaneous sensibility is greatly impaired, pain in the muscles and joints, neuralgia, and marked headache localized in most instances in the occipital region occur in about one-half of the cases. These are due to the accumulation of toxic intermediate waste products in the blood, owing to the deficient antitoxic power of the latter.

The senses of smell and taste are commonly impaired or perverted, the patient complaining of foul odors, a bitter or acid taste, etc. Vertigo is a relatively frequent symptom. The vision is occasionally dimmed and optic atrophy has been observed. Tinnitus aurium is not uncommon, and the hearing is impaired in the majority of cases.

Hæmorrhages from one or more organs are common. Epistaxis, hæmoptysis; bleeding at the gums, which may prove severe on extracting a tooth; intestinal, uterine, and even cerebral hæmorrhages may occur. Probably the most common, however, is menorrhagia. Postpartum hæmorrhages are also common in these cases. The menstruation is irregular, as a rule, and often ceases altogether until appropriate treatment procures recovery. This condition is mainly due to the poverty of the blood in fibrin ferment, as shown by the prolonged coagulation time, and to the relaxation and pseudo-fatty changes ("pseudo" because they are temporary) throughout the cardiovascular system. It is aggravated by the weak heart action, especially in advanced cases, in which the heart is deprived of the aid the adrenal secretion affords its muscular elements. The pulse is slow and weak and sometimes quite difficult to locate. The *vis-a-tergo* motion of the blood in the peripheral capillaries is slowed to a marked degree as soon as the disease has reached beyond the initial stage. To this is mainly due, in fact, the dense œdema which is the most evident characteristic of the disease.

The specific gravity of the urine varies but little; on the whole, however, it is somewhat reduced; but the urea excretion is diminished in most cases, and markedly so when the disease is advanced. In the latter case, both albuminuria and glycosuria (probably alimentary) may occur, but disappear when the thyroid treatment is instituted. Casts are also found in advanced cases.

Myxœdema progresses slowly, a case lasting, as a rule, from six to twenty years, unless the patient is carried off through some intercurrent trouble, which is often the case. Tuberculosis and pneumonia are the infections to which they seem to be especially vulnerable—owing to the enfeebled condition of their autodefensive resources. Nephritis, pericarditis, and cerebral hæmorrhage seem to be next in the order of frequency. Periods of amelioration sometimes occur, but sooner or later the patient relapses into his previous state, and gradually dies of exhaustion. Rarely, especially in young adults, the disease may run its course in less than six months.

Acute myxœdema with prompt death may occur as the result of sudden arrest of the functions of the thyroid. In a case reported by Lloyd, the disease proved fatal in a few days. In another instance it occurred as the result of an injury to the thyroid. It may appear as a sudden complication of goiter; it is probable, however, that under these conditions we are dealing with some toxæmia of thyroid origin rather than with true myxœdema, since we know that even extirpation of the thyroid does not produce death rapidly.

The thyroid gland is distinctly reduced in size in about 75 per cent. of the cases of myxœdema, its outline being hardly discernible by palpation in some of these. Conversely, some are abnormally large at first, and may then gradually atrophy irregularly, the portion which fails to decrease in size being resistant to pressure.

ETIOLOGY.—Women are more liable to the disease to a considerable extent than men, *i.e.*, it occurs about six times in women to once in men, and it may develop at any time of life, though the period between the thirtieth and sixtieth years shows by far the largest proportion of cases. There is a marked familial influence, some families showing several cases. While hypothyroidia, alcoholism, and syphilis are likely to be the predominant parental factors in progressive hypothyroidia or true myxœdema, tuberculosis and neuroses are met with much more frequently in the family antecedents of the patient. The main causes appear to be rapid child-bearing, the menopause, worry, mental shocks, and injuries, especially to the head. Neoplasms, fungi, and entozoa capable of destroying or inhibiting a sufficient area of the gland have also been known to cause the disease.

PATHOLOGY.—The characteristic lesion in the thyroid is atrophy, due to the development of fibrous tissue, the glandular elements of the organ being reduced in proportion. It may follow local inflammatory lesions in connection with acute articular rheumatism, erysipelas, syphilis, actinomycosis, cancer, an acute thyroiditis, local injuries, etc., which serve to destroy a part of the glandular parenchyma, and annul in proportion its secretory functions. Excessive child-bearing, shock, and the menopause can hardly be regarded as causes of an inflammatory process, however, and it is probable that we are dealing, in this connection, rather with functional exhaustion of the organ, or with an endarteritis or periarteritis of its vascular supply.

TREATMENT.—The use of thyroid gland in this disease, introduced by Murray, is rightly considered one of the great steps in modern medicine. As in the case of hypothyroidia, however, large doses should not be used; this rule is all the more applicable to myxœdema in view of the marked relative weakness of the subjects. Again, exertion of any kind should be avoided while taking thyroid; two of Dr. Murray's cases died of syncope during active exercise taken too early after a prolonged treatment, though it must be said that he used larger doses than are now recommended. One grain (0.066 Gm.) of the desiccated thyroid, three times daily, suffices to begin with; this dose may be gradually increased ½ grain (0.033 Gm.) until 2 grains (0.132 Gm.) are given at each meal, and until the temperature is raised to normal. If this is exceeded the dose should be reduced to 1½ grains (0.099 Gm.) or less. The pulse should also be watched, an increase of fifteen beats indicating the need of reducing the dose. I prefer these divided doses to the single daily, but correspondingly larger, dose recommended by some observers, as the latter has seemed to me to increase the likelihood of untoward effects. Cases vary considerably in this respect, however, and the tolerance of each case should be carefully studied. The patient should spend his time in an armchair during the day, at first, if possible, in the open air, and begin to walk around only when his temperature and pulse become normal.

The effect of the remedy is to cause gradual disappearance of all the morbid symptoms, but if its use is discontinued they as surely return. Two grains (0.132 Gm.) daily suffice, however, to perpetuate the recovery in most instances. Before the introduction of the thyroid treatment, the disease was fatal in practically every instance. Grafting of thyroid is now used successfully to prevent the need of constantly taking thyroid gland. The measure is described on page 200.

When the asthenia is marked and the heart, as is usually the case under these conditions, is considerably dilated, a small dose of digitalin, $^1/_{20}$ grain (0.0033 Gm.), three times daily, or the desiccated suprarenal gland of the U. S. P., or, better, the pituitary gland, 1 grain (0.066 Gm.) during meals, greatly hastens the curative process.

INFANTILE MYXŒDEMA, OR CRETINISM.

Although cretinism is, like myxœdema, due to loss or impairment of the functions of the thyroid apparatus, its symptomatology differs in many respects from that of myxœdema, because, as previously stated, it occurs during the period of life when growth and development, physical and mental, are most active, *i.e.*, between birth and puberty, whereas myxœdema includes only cases that occur after puberty. In cretinism we witness the results of defective oxidation and metabolism of cellular proteids and fats at a time when the building up or anabolic phase is exceptionally active, and, as a result, arrest of physical and mental growth. The following definition seems to me to include the main features of the disease:—

Infantile myxœdema, or cretinism, is a functional disease due to marked or complete hypothyroidia during the period between birth and puberty. It is due to deficient oxidation and is characterized by retardation of physical and mental development, the main symptoms of which are: stunted growth, the cretinic facies with flattened nose, thickened lips and tongue, a harsh skin, and more or less advanced idiocy.

SYMPTOMATOLOGY AND PATHOGENESIS.—The disease may develop *in utero*, but it is seldom recognized before the first month. The attention is drawn to the child through the fact that it fails to grow at the average rate either physically or mentally. Its tongue is then noticed to be unusually thick—sufficiently so, in some instances, to project beyond the lips at all times, fill the oral cavity, and interfere with the respiration when the child lies in the recumbent position.

Closer examination then reveals the symptoms witnessed in adult myxœdema. The "jelly-like swelling" of Ord, coupled with the yellowish, white, or waxy pallor, the rough, dry, and scaly skin, so unlike that of a normal child, is clearly defined, though the puffy face retains some of its smoothness. The fontanelles remain patent unusually long. The features of the cretin are, as a rule, repulsive, though pitiful. The swollen, often wrinkled brow; the puffy lids, which reduce the watery eyes to mere slits; the "saddle-back," or depressed, nose with its wide and thick alæ; the swollen, erect ears; the large and drooling tongue between thick lips, and the aged appearance constitute a picture which causes all cretins to resemble one another, and which one is not apt to forget.

Again do we meet the evidences of deficient metabolism and nutrition. The hair is thin, but coarse and brittle, the eyebrows and eyelashes being also scant and often absent. In some cases the hair may be thick, but likewise coarse and deprived of luster, resembling tow in texture rather than human hair. The nails are very short, thin, streaked, and brittle. The teeth, which may be represented by a few sharp points, as in a teething infant, are irregular and tend to early decay, the second dentition, which often fails to occur at all, being long delayed at best, the teeth being no less liable to caries, and no less ill-shaped, than their predecessors.

The body and extremities show not only arrested development, but the effects of irregularity in this morbid process, the different parts of the body, the bones especially, showing considerable disproportion. The trunk, though small as compared to the head, may be relatively massive, the back arched at the waistline and perhaps scoliotic, the abdomen, on the other hand, projecting forward considerably, with, often, an umbilical hernia. Conversely, the legs are short and more or less bowed; their cutaneous covering having developed to a greater degree and thickened, it forms folds which tend further to distort these members. The same perversions of local growth exist elsewhere, but to a less evident degree. The hands are broad, spade-like, and the fingers pudgy and stiff, a condition reproduced in the feet, the toes of which are kept apart by the thickened skin. The supraclavicular region is usually the seat of thick pads, which sometimes encircle the neck, filling the depression between the latter and the shoulders. When a goiter is present, as is usually the case in the endemic form—though the gland is practically functionless—the distortion of this region of the body is striking.

The defective oxidation due to the inhibited thyro-adrenal functions is well shown by the subnormal temperature, the cold surface, the extremities being sometimes livid, and the marked diminution of nitrogen excretion. The blood-pressure is correspondingly lowered both owing to the deficiency of the adrenal product, which deprives the blood-vessels of its direct tone-sustaining effect, and because the rate of metabolism in the cardio-vascular muscles is slowed. Both these factors and the ever-present anæmia cause general vaso-dilation and low tension. All muscular elements in the body being influenced in the same way, the child is weak, walks in a wobbly, slow, inco-ordinate way, and, in some instances, is quite unable to stand or to sustain its head, which then droops on the chest.

A similar condition of the muscular coat of the intestines practically prevents peristalsis, with inveterate constipation as result, the bowels being relieved only by an occasional outburst of diarrhœa, unless appropriate measures, enemas, purgatives, etc., are resorted to periodically. This ultimately leads the patients to realize that semifluid or fluid food is alone well borne by the child, which has to be fed with a spoon, the whole alimentary canal from mouth to anus being much in the same condition as the skin—*i.e.*, deprived of much of its normal fluids—another source of constipation.

The genital organs, both the ovaries and testes, remain imperfectly developed, though not necessarily infantile. Occasionally the genital organs are hypertrophied and the sexual instincts are enhanced. Their offspring tend to be feeble-minded, however, and are liable to excessive mortality. Menstruation often fails to appear, or is scanty; or it may be profuse, and even hæmorrhagic, owing, as in myxœdema, to deficiency of adrenoxidase in the blood and to the imperfect coagulating power this entails. Epistaxis and bleeding at the gums are also commonly observed.

The urine shows but little change, though the urea excreted is below normal. In very marked cases, albumin and hyaline casts have been found periodically, doubtless owing to the autointoxication resulting from retained excreta in the intestinal canal. The thoracic and abdominal organs do not seem to be involved in the morbid process.

The mental state of the child depends upon the severity of the case. In some it is not far removed from what Roesch has termed a "human plant," even the intelligence common to the higher animals being wanting. The child fails to recognize its parents or any person about it, or even a person from an object, and nothing, even toys, interests it in the least. It neither weeps nor laughs. It is absolutely apathetic, sits quietly without manifesting any special wants. It may, however, show signs of hunger or thirst, either by crying like an infant or by grunts or inarticulate sounds. In a higher grade, a few words may be spoken, there is recognition of parents and familiar faces and even a show of affection for them, but beyond the limited vocabulary no progress can be made, even the alphabet being beyond them. Still higher grades may speak fairly well, be free, though slow and deliberate, in their movements, etc., but fail to develop thereafter, even if they attain old age, which is not often the case.

The brothers Wenzel have divided these cases into three classes: the *cretins,* who are unable to speak, and lead a purely vegetative life; the *semi-cretins,* who are simple-minded, but whose language is limited and imperfect; and the *cretinoids,* who are endowed with some intelligence, but show the physical signs of cretinism. There is another type, the *mongolian,* called thus because of their slanting eyes, which closely resembles the cretin of a higher order, but this type shows more intelligence and seldom yields to the effects of thyroid preparations.

The thyroid, in about two-thirds of the cases, is more or less atrophied, to such a degree in some that it cannot be detected by palpation. In the remaining third, and usually in the endemic cases, there exists a more or less developed (sometimes voluminous) goiter.

ETIOLOGY.—It becomes necessary in this connection to distinguish between the two general classes, endemic and sporadic cretinism.

Endemic cretinism, often a family disease, and observed in a number of cases in special localities, is believed to be due to some chemical substance or micro-organism peculiar to the waters available in those regions.

This type has been connected with special localities by proofs from various directions. Not only is cretinism common in these regions, but normal individuals may, on moving to them, have cretinic children therein, and normal children in healthy regions. Again, animals from the latter were found to develop goiters (the preliminary cause of endemic cretinism) in the contaminating districts by drinking their water, while this water carried afar to healthy localities and given to dogs as sole beverage also caused goiter in these animals. Whether it is a mineral salt, a vegetable mold or some other pathogenic micro-organism is not established, but for the time being the germ theory seems to prevail.

The question of heredity in these cases is a debated one. We have seen under "hypothyroidia" that syphilis and alcoholism tend to leave their imprint upon the thyroids of descendants. Some oppose this view in respect to cretinism on the ground that the positive signs of cretinism only appear when the child is weaned, and contaminating water is given to it. But this is obviously wrong: Cretinism can readily be detected in a child one month old and earlier by observers who are thoroughly familiar with the morbid effects of hypothyroidia. The latter condition in the mother is also well known to result in hypothyroidia in her offspring—a fact which brings us back to any maternal defect inherited, such as hypothyroidia, syphilis, alcoholism, etc., that may be present as the origin of the hypothyroidia in the child. In other words, there is at present no sound foundation for antagonism to the prevailing view that endemic cretinism may be congenital in a certain proportion of cases.

Sporadic cretinism, which has also been termed "cretinoid," or *"myxœdematous, idiocy,"* and *"cretinoid pachydermia"* occurs in any country, in localities that are entirely free from cretinism, and in healthy families. It is mainly due to some lesion of the thyroid caused by an acute febrile disease or some intoxication capable of inhibiting or arresting its functions, either before or after birth.

How a general infection can produce such lesions in the thyroid is admittedly unknown. From my viewpoint, it finds its explanation in an autodigestive process similar to that which occurs in the pancreas under certain conditions. As previously stated, I have attributed to the thyroid secretion properties similar to those of Wright's opsonins, a view recently sustained by Marbé and Stepanoff, at the Pasteur Institute. The antitoxic and antigerm constituents of the blood circulating in the thyroid (and parathyroids, which may also be the seat of similar lesions), it is obvious that undue accumulation of thyroid secretion in the organ itself will oversensitize its own parenchyma or its vascular elements or both, and render them vulnerable to proteolysis—along with any germ or toxin that may be present in the organ. The autodigested areas are replaced by fibrous tissue, and a process of cirrhotic atrophy is started which sooner or later annuls the functions of the organ.

The diseases which have shown themselves to be the most frequent causes of sporadic cretinism are typhoid fever, scarlatina, pneumonia, and pertussis—the identical series which proves most prolific in the genesis of the infantile encephalopathies, another source of idiocy, but in which the cerebral lesions are the direct pathogenic factors.

PATHOLOGY.—The end lesions are the same in both forms. In the endemic form there is a marked proliferation and overgrowth of interstitial tissue or connective tissue, causing both enlargement of the gland—goiter—and obliteration of the glandular tissue. Some glandular tissue usually persists; even this remnant, however, shows evidences of degenerative change.

The symptomatology of both forms indicates clearly, we have seen, that deficient oxidation, metabolism, and nutrition underlie the resulting general physical phenomena. This applies as well to the mental phenomena, symmetrical arrest of development affecting more or less all the elements of the brain. There are occasionally found localized lesions of the nature of infantile cerebropathies, porencephaly, etc., but it is probable that these are concomitant changes rather than components of the typical picture of cretinism *per se*. Briefly, we are dealing with arrested nutrition and development of the brain as a result of the absence of the secretion which sustains these fundamental processes.

TREATMENT.—Before the introduction of thyroid gland in the treatment of this distressing condition, there was practically nothing to be done. While its use must be continued, relapse (excepting the body growth) occurring invariably without it, though, as a rule, with much less intensity, the fact remains that the changes produced in the child, particularly in sporadic cases, are truly marvelous. As early development of the disease inhibits the mental development accordingly, the later in childhood it appears, the better are the results of treatment, in so far as the intelligence is concerned. The physical restoration is not materially influenced by the age at which the disease first appeared. Children grow with surprising rapidity in some instances, over one inch per month in some cases, until the normal stature of the corresponding age is reached. The brain responds more slowly; but considerable intelligence is gained, though it does not reach, as a rule, that of normal children. They learn slowly and develop only very gradually their vocabulary. They should be gently assisted in this direction.

When the thyroid treatment is instituted the case should be carefully watched, as the tolerance varies greatly in different children. They should be kept from any violent exercise lest heart-failure occur. Another important reason for this precaution is the fact that the growth of the skeleton is so rapid that the bones tend to soften, and, therefore, to yield and bend. The tibia and fibula are especially exposed; braces should be applied to offset this tendency if it shows itself, until the normal height of a child of a corresponding age has been attained. Syrup of calcium lactophosphate of the U. S. P., one teaspoonful or less, according to the age, is a useful adjuvant to thyroid gland in this connection. This is accounted for in the opinion of Parhon and Papinian[11] and others, based on many published facts, that the thyroid gland plays an important rôle in the assimilation of calcium. Thymus gland 5 grains (0.3 Gm.) *t. i. d.* is also useful.

Large doses are not only dangerous, but they inhibit the beneficial process. Again, it must be remembered that the thyroid active principle is cumulative in the sense that the organism will utilize a certain quantity—which varies with each case—and that any excess may prove toxic. This stage may be reached early in one instance and late in another. I have seen it produced in three weeks with 2-grain (0.132 Gm.) doses; conversely, in a case reported by Freund in a girl of 14 years, 6 grains (0.396 Gm.) daily in divided doses caused a sudden rise of temperature to 104° F., a pulse of 160, rapid breathing, and death the next day, though she had been taking the same agent nineteen months. The *danger signals* are rapid pulse, vertigo, general weakness, pains in the back and limbs, syncope, and, if the intoxication be severe, nausea and vomiting, a marked rise of temperature, and collapse. When any untoward effect occurs, cessation of the remedy a few days suffices. They are more likely to appear when the preparation used is old, a fact which suggests that it may have undergone putrefactive changes when long kept.

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[11] Parhon and Papinian: Románia medicala, 1904, cited in "Sécrétions Internes," p. 17, 1909.

An infant can be given ½ grain (0.033 Gm.) daily of desiccated thyroid, and a child of 2 years, twice daily, and older children thrice daily, or 1 grain (0.066 Gm.) can be given at dinner and another on retiring. I have never seen such doses produce untoward effects, the recumbent position after the second dose, as urged by Murray, preventing them. When it is necessary to increase the dose, the patient should be seen frequently. As much as 5 grains (0.33 Gm.) have been given three times daily with safety; but it must be remembered that the preparations now available are better and more efficacious. The preparation I now use is Burroughs, Wellcome & Co.'s standardized desiccated gland substance (in tabloids), which contains 0.2 per cent. of iodine in organic combination. Cretins usually stand larger doses than others. A good guide in them is the temperature, which tends to rise to normal; as a rule, the dose that will do this suffices to bring about the desired results. When this is attained, 1 grain (0.066 Gm.) on retiring suffices to prevent recurrence. But it must not be neglected; otherwise, the disease will certainly return.

The younger the patient, the more marked the improvement, as a rule. In adult cretins, the results are meager if any at all are obtained. The improvement is much more marked in sporadic than in endemic cases, owing probably to the fact that up to the onset of the causative disease physical and mental growth had proceeded normally. In the Mongolian type, the thyroid treatment is useless.

Grafting of thyroid tissue to render the constant use of thyroid preparations unnecessary has been tried by various investigators. It is only in recent years, however, that a promising method has been [illegible] by Christiani,[18] of Geneva. The conditions are that only normal and living tissues be used; that the grafts be small (about the size of a grain of wheat), but

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[18] Christiani: [illegible]

very numerous; that they be inserted in very vascular subcutaneous cellular tissue, and that only human thyroid be employed. This makes it possible to obtain small grafts from a removed goiter containing areas of normal tissue, and to transplant them into the cretinous subject. The tissue can be kept alive an hour in physiological saline solution. A very sharp instrument should be used to cut the grafts to avoid crushing them. They are then introduced *in situ*, where they gain a perfect foothold, becoming perfect thyroid parenchyma. More recently, Charrin and Christiani[13] obtained good results with sheep's thyroid. Six months after the operation, the patient (a case of operative myxœdema) became pregnant, and it was found that each graft became enlarged, in keeping with the physiological process which occurs normally in the gland proper under similar circumstances. Christiani[14] reported distinct improvement in 60 per cent. of his cases, which included myxœdema, cretinism, dwarfism, etc., remarkable results in 31 per cent., and no result in 6 per cent. The most striking results were in the various types of cretinism.

MYXŒDEMATOUS INFANTILISM.

This disorder, first attributed to the thyroid by Brissaud, resembles cretinism very closely, but its retention as a separate class is warranted by the fact that the arrest of development manifests itself mainly by the persistence of the characteristics of childhood, physical and mental, without the evidences of true idiocy, and often without dwarfism. The thyroid apparatus, either through inadequate development of congenital origin, organic lesions, especially sclerosis, acquired in the course of acute infections during infancy, or from some other cause, is unable to supply enough of its secretion to subserve the needs of both metabolism and growth (which involves an excess of metabolic activity), and the latter ceases, while normal metabolism, enough to sustain the vital process, continues.

SYMPTOMATOLOGY AND PATHOGENESIS.—The worst cases, in which myxœdema predominates, are virtually instances of cretinism of a mild type. The patient is short, thick set, and obese, though child-like in shape, and may look old for his age. The face appears bloated, rounded, pale, and wax-like, a reddish patch being sometimes present below the cheek bones. The nose squatty and pugged, and the mouth large; the latter is usually open,—a fact accounted for by the almost invariable presence of adenoids, hypertrophy, and infiltration of the nasal mucosa and tonsils. The tongue, as in the cretin, may be thickened and the lingual tonsil likewise, rendering speech thick and difficult. The hair may be profuse, though coarse and lusterless, but about the eighteenth year it begins to fall in patches, leading, in most instances, to alopecia. In most cases hair fails to grow on other parts of the body. The skin is tense, owing to infiltration, and is also dry, because of deficient action of the cutaneous glands, and it feels rough and scaly to the touch. Pruritus is often complained of.

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[13] Charrin and Christiani: Le bulletin médical, July 11, 1906.
[14] Christiani: Bull. de l'Acad. de méd., vol. lviii, 1907.

The teeth remain infantile, as a rule, and decay early. The abdomen is unusually prominent and hard in all cases, owing, mainly, to the stubborn constipation which causes retention of gas and fæces, the latter being only voided in some cases by engorgement and to relaxation of the abdominal muscle. The constipation is also mainly due to the loss of tone of the intestinal muscular fibers and the paucity of succus entericus. Enuresis is commonly observed. Although the respiration is apparently normal there is deficient oxidation; the extremities are cold and are readily affected with chilblains in cold weather. The face and extremities may even be cyanotic and the patient complain of constantly feeling cold. Actual hypothermia is a common feature of these cases. The part played by the thyroid in this phenomenon is well shown by the fact that Beebe[15] found that "by the administration of thyroid to a cretin or patient with myxœdema it is possible to increase the absorption of oxygen from 20 to 75 per cent."

The difference between this form and true cretinism lies, as stated, in the fact that idiocy does not occur. The child may not be bright or even normally intelligent, having been slow to talk and shown deficiency at school, particularly in spelling, grammar, and arithmetic, but it is, nevertheless, quite able to hold its own for all ordinary needs; the face, in fact, unlike that of the cretin, bears an expression of intelligence. Yet the intellect retains the characteristics of childhood, both as to ideas, judgment, and emotions, a patient of twenty years, for example, preferring the company of children below ten to that of young men of his own age. These patients may show a proclivity to lie, steal, start fires, etc., especially when under the evil influence of designing normal individuals. Any unlawful act they may commit is due, in most cases, more to lack of judgment and inability to resist suggestion and a desire to please others than to an inherent proclivity to crime. Others are excitable, turbulent, and rough, and frequently break anything that is at all fragile; here, again, the element of willful harm is absent, muscular tremor and inability to prevent movements of the hands or fingers—as in athetosis—being the underlying cause of the defect.

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[15] Beebe: *Loc. cit.*, p. 659.

The heart is excitable, a slight emotion sufficing to cause violent "palpitations" and tachycardia. This is mainly due to a deficiency of adrenal secretion. Dilatation of the heart from the same cause is often witnessed. The veins also show a marked tendency to dilate, the veins of the extremities and the hæmorrhoidal veins particularly. Varicocele may also exist. In a case seen through the kindness of Dr. W. Egbert Robertson, a sprig of thick veins spread upward over the mons veneris and coincided with undeveloped testicles and total absence of hair over the genitalia, in a young man of twenty years. Hæmophilia is frequently noted, an indirect result also of the hypothyroidia, since thyroid gland given orally counteracts hæmophilia by increasing the coagulation time. Epistaxis, menorrhagia, and metrorrhagia are also observed in some cases, the two latter phenomena where menstruation has developed at all, which is often not the case, coinciding with non-development of the breasts and pubic hair. The penis and testicles often remain rudimentary even when the male reaches full adult age, and his general shape and high-pitched voice recalling those of a woman.

In a still higher type of infantilism the signs of myxœdema are hardly discernible. The growth may even exceed that of the average individual. Such cases are usually plump and even portly; as in the preceding form, the abdomen tends to be large, but the limbs are well rounded, recalling those of a woman, with fair skin, a high-pitched, or infantile, voice to complete the resemblance. The face, axillæ, and pubis are free of hair; the penis and testicles small and rudimentary. Mentally "he is simply an overgrown child," wrote Meige,[16] who gave us a close analysis of these cases. "These children, who should long before have reached the reasoning period of their lives, play with toys, laugh at a childish prank, cry for practically nothing, become angry as readily, are subject to ridiculous frights, and call their mamma under the influence of the least emotion." In the average case, however, this truly infantile type—recalling the behavior of a child of but two or three years—is better exemplified by one of seven or eight years, though he be perhaps actually beyond his twentieth year.

The feminine attributes are sometimes very marked in the male, the breasts, thighs, and general conformation resembling closely those of the female, constituting the "feminine" type. In the female, in whom infantilism occurs less frequently, the body preserves the attributes of childhood, *i.e.*, it fails to undergo the normal changes of puberty. Though tall, perhaps, the body shows no development on sexual lines: the breasts remain small and flat, no hair grows in the axillæ or over the pubis, the trunk remains cylindrical, and the hips and nates flat. The uterus and its adnexa also fail to develop, and menstruation fails to appear. Some cases tend even toward the male sex, constituting "masculinism," the voice, the physical outline, assuming a masculine type.

DIAGNOSIS.—From this type, which belongs essentially to the domain of the thyroparathyroid apparatus, must be distinguished several types which do not.

Lorain Type of Infantilism.—In a type described by Lorain, in 1870, the dwarfism is symmetrical in the sense that the ultimate products are symmetrical, miniature men—this form being practically always observed in the male. No myxœdematous symptoms are present; the genitalia are usually normal, though the pubic and axillary hair is wanting, and notwithstanding their diminutive stature and their slender physique, their facial appearance and expression, and their intelligence are usually quite up to the average. They depart in no way from their fully developed fellow-men, in fact, except in the stature. As shown mainly by Meige,[17] this type is not due to thyroid insufficiency, but to anangioplasia, *i.e.*, defective development of the arteries and premature ossification. It is usually ascribed to parental hereditary syphilis, tuberculosis, alcoholism, and other debilitating disorders. Thyroid preparations in this form are of no value.

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[16] Meige: Revue Intern. de Méd. et de Chir., Mar. 25, 1896.

Mongolian Infantilism.—This type is characterized by Mongolian features, and particularly the slanting eyes. These features occur at birth, and are not traceable to syphilis, tuberculosis, alcoholism, etc., as in the Lorain type, but rather to prolonged deliveries—which account in some cases, at least, for the flat skull or bulging forehead—or to strong mental emotions during pregnancy. They are not morose or torpid like the myxœdematous cases and are usually amiable and well behaved. Curiously enough, all show a marked predilection for music and signs of unusual development of the musical sense. The tongue is usually quite thick and heavy, and the hands square and flat, the latter accounting for the clumsiness which characterizes all these cases. They usually suffer from some chronic respiratory trouble, and are apt to die early of some intercurrent infection. Their undeveloped size, their Mongolian facies, the bulging forehead, and their feeble-mindedness render the recognition of these cases quite easy. Thyroid preparations are of no avail.

Achondroplasia, or Fœtal Rickets.—This type of dwarf, unlike the myxœdematous type, does not show mental deficiency, but many of the characteristics of cretinism: the relatively large head, the saddle nose, the short and bowed limbs, the prominent abdomen, and the marked lordosis. But the arms and legs are, unlike the other types, which all show some degree of symmetry, entirely too short for the body, the finger-tips never reaching the level of the hips. Again, the long bones are usually bent and deformed. The skull is unduly developed and is out of proportion with the face, which is then made to appear small. The eyes, lids, and tongue may resemble greatly those of the cretin, but the hair is normal and usually abundant, and the skin soft and well nourished. These characteristics, the fact that the mental faculties are quite normal, and the ineffectiveness of thyroid treatment render the identification of achondroplasia quite easy.

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[17] Meige and Allard: Nouvelle Iconog. de la Salpêtrière, No. 2, 1896.

TREATMENT.—The only measure of any value in myxœdematous infantilism is the use of thyroid preparations. The treatment recommended for cretinism being as applicable here, the reader is referred to page 198. The younger the patient, the greater are the chances of improvement. After puberty has been reached, the results, in so far as the mental status is concerned, are seldom satisfactory.

THYROID HYPERÆMIA AND THYROIDITIS.

This is a very important disorder mainly because of its causative influence upon the conditions just reviewed, *e.g.*, hypoparathyroidia, myxœdema, and cretinism, and the whole gamut of morbid effects of deficient functional activity of the thyroparathyroid apparatus. It is generally recognized in its acute form when the inflammatory phenomena are very marked, but, unfortunately, it is not only in this class of cases that lesions in the organ are provoked. The structure of the thyroid is such, and the quantity of blood circulating through it is so great, that a high blood-pressure, such as that which occurs during high febrile processes, is sufficient to produce areas of interstitial hæmorrhage in the interlobar connective-tissue spaces, which form as many sclerotic areas wherever the damage done has been sufficiently great. As nature provides an excess of thyroid tissue over and above the needs of the organism, however, inhibition of a proportion of the gland below this limit may prove harmless, but if the sclerosis happens to exceed this limit the result is a more or less marked hypothyroidia (or hypoparathyroidia if the parathyroids are involved, which is at least sometimes the case) corresponding in severity with the proportion of thyroid tissue sacrificed. Indeed, we have seen that in all the disorders treated so far in the present chapter sclerosis of the thyroid, with its resulting atrophy, was by far the most prominent pathogenic lesion.

The graver condition, acute thyroiditis, is fortunately comparatively rare. Moreover, while simple hyperæmia, even when attended by interstitial hæmorrhage, is seldom recognized, acute thyroiditis is attended by severe local and general phenomena, which make it possible to identify it early, to meet it therapeutically and avoid disastrous results. Acute inflammation of the thyroid—apart from that due to the presence therein of goiter, cancer, etc.—is usually provoked by invading bacteria in the course of infections, notably: diphtheria, typhoid fever, scarlatina, measles, parotitis, tonsillitis, erysipelas, pneumonia, pertussis, dysentery, rheumatic fever, puerperal fever sepsis, orchitis, and influenza. It has also been attributed to the action of poisons, constituting what has been termed "toxic thyroiditis"; iodine and the iodides have also been known to cause it along with other signs of iodism. In these inflammatory disorders the glandular tissues undergo marked changes, including desquamation and degeneration of the epithelium, besides the interstitial sclerosis met with in the form previously described. If the area thus affected is large, the functions of the gland may become sufficiently impaired to constitute marked hypothyroidia, which, we have seen, may, in children, arrest general development of both the body and mind. Shields[18] witnessed an instance in which thyroiditis lasting one week led to complete atrophy of the organ and to typical cretinism. In a case reported by Bonney[18a] the left lobe was converted into an abscess cavity.

SYMPTOMATOLOGY.—Though capable of doing considerable injury to the gland, the acute hyperæmia attending infectious diseases gives rise to few tangible phenomena, *i.e.*, slight swelling of the neck, sensitiveness to pressure, and, perhaps, slight pain during deglutition. Unless looked for, they will seldom be discerned, as they do not cause sufficient discomfort to attract the attention of the patient.

In acute thyroiditis the onset, usually ushered in by a chill, is generally sudden; the most marked symptom is difficulty in swallowing with, sometimes, neuralgic pain which radiates widely in various directions, the ears and neck, even to the arms and occiput; this is sometimes very severe, particularly during deglutition and on moving the head from side to side. If the whole gland is involved and the swelling, which is often the size of a hen's egg, is marked, severe dyspnœa and even cyanosis may occur, owing to pressure of the inflamed organ upon the trachea. Paralysis of the recurrent laryngeal may occur and produce hoarseness and paroxysms of suffocation, but the hoarseness and cough are more likely to be due to involvement of the larynx in the inflammatory process. Œdema of the glottis may also occur, as in cases reported by Lewis and O'Neill.[19]

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[18] Shields: N. Y. Med. Jour., Oct., 1898.
[18a] Bonney: London Lancet, July 15, 1911.

The identity of the inflamed organ is readily established by causing the patient to swallow, when the tumor will rise, provided the head is not bent backward, which will immobilize the organ. Headache is often present and epistaxis occurs sometimes, owing to pressure of the enlarged thyroid upon the cervical veins and the passive cerebral congestion this produces. Carotid pulsation has also been observed by Broca. The surface of the organ is sometimes quite congested. There is more or less fever during the acute stage; it is sometimes quite high notwithstanding the absence of suppuration—a fact which is ascribable to the excessive production of thyroiodase. Tachycardia independent of temperature has also been noted by Parisot.[20] As observed by Jeanselme, the coagulating power of the blood is greatly increased. The morbid process lasts, as a rule, but a few days, the swelling subsiding completely in most instances. Occasionally a certain amount of enlargement may persist. Forty per cent. of the cases terminate in resolution, *i.e.*, without suppuration.

When an *abscess* is formed the course of the morbid process is more protracted. A single abscess rarely occurs, the glandular mass being studded with numerous purulent foci, which, if close one to the other, tend to run together. Each abscess tends to break through the adjacent soft tissues, including the skin. The trachea and œsophagus may therefore be invaded by a purulent stream when rupture occurs. Metastatic abscesses may also appear in the cervical cellular tissue. When spontaneous rupture occurs through the skin, or when the abscess is surgically evacuated, the inflammatory process recedes rapidly. When, however, it is left to itself, the purulent infiltration of surrounding parts may give rise to serious complications, by involving, besides the trachea and œsophagus, referred to above, the mediastinum, the pleura, and the lungs proper, causing septic pneumonia, and also the large vessels of the neck and chest and thus causing pyæmia. Thyroid abscesses bleed readily and are sometimes the source of severe capillary hæmorrhages.

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[19] Lewis and O'Neill: Jour. Amer. Med. Assoc., Nov. 12, 1910.
[20] Parisot: Presse Médicale, May 7, 1910.

Chronic thyroiditis may follow the acute type, either through perpetuation of the infection in some small portion of the gland or the formation of a sinus which fails to heal. In the majority of instances, however, it occurs concomitantly with chronic processes, such as syphilis, tuberculosis, echinococcus cysts, actinomycosis, etc. The prognosis in these cases is less favorable than in the acute form, since more or less impairment of the functions of the organ follow the destructive action of the abscess upon the glandular tissues owing mainly to the fibrous induration it entails in various parts of the organ. Both the acute and chronic types are prominent causes of hypothyroidia with its long train of morbid results, ranging from cretinism through its many modalities to the milder types of myxœdema described.

Diagnosis.—In the acute form, the increased volume of the gland, which sometimes becomes greatly enlarged in a few hours, the sensitiveness to pressure, and the radiating pain, all located in the region of the thyroid, coupled with the fact that, on swallowing, this organ, *i.e.*, the seat of all these acute symptoms, moves up and down, render the diagnosis quite easy in well-marked cases. When, as is often the case, the inflammation is unilateral, especially if œdema of the tissues prevails, it may resemble mastoiditis or parotitis and has, in fact, often been taken up for the latter disease. Its connection with a mobile structure on the other side of the neck, however, renders the differentiation possible. If abscesses form, fluctuation is sometimes discernible. Œsophageal abscess in the neighborhood of the thyroid furnishes much the same symptoms, but the mobility of the gland during deglutition makes it possible to identify it as the seat of abscess.

Treatment.—The prevention of acute thyroiditis, even in its milder forms, is an important feature in this connection, when we consider its pernicious effects upon development of the child and upon the general welfare of the individual at all ages.

As previously stated, the main cause of the lesions is the excessive proteolytic activity of the intrathyroidal plasma, owing to the identity of the organ as the source of the substance which, as I have pointed out, is the homologue at least of Wright's opsonin—*i.e.*, the thyroiodase. The presence of bacteria in the thyroid brings to it, as elsewhere, all the defensive constituents of the blood, both fluid and cellular. The excess of opsonins increasing the vulnerability of the thyroidal tissues to the proteolytic activity of these antibodies, however, these tissues yield readily to the destructive action of the latter. The aim, therefore, should be to prevent this complication in the course of febrile infections.

Two measures of value are at our disposal in this connection. The first of these is the local application of cold. The thyroid should be carefully watched for any complication, and if it becomes sensitive or swollen, or the patient complains of pain in the thyroidal area, cold compresses should be applied over it. The effect of cold is to reduce local temperature and through this the activity of the proteolytic enzymes which the antibodies of the blood contain. In other words, it is not bacteria which do the damage, but the excessively active germicidal substances they invite into the gland, and by reducing this activity with the aid of cold the *excess* of digestive power is antagonized. That the bacteria are less violently attacked under these conditions is obvious, but it is far better to allow the blood-stream to transfer the germs elsewhere in the body for destruction, *i.e.*, to the general circulation, where their destruction can proceed without compromising the integrity of any tissue so vital to the welfare of the body as the thyroid.

The second measure is the free use of physiological saline solution, either by the mouth, rectum, or subcutaneously, to reduce the viscidity of the blood. Not only does this counteract excessive proteolytic activity of the antibodies which underlies their destructive action on the thyroid and other tissues and cells—the underlying causes of hæmolysis and autolysis—but it facilitates osmosis and therefore the circulation through the thyroid, which has been fittingly compared by Bérard to a sponge, so replete is it with blood. Another advantage of the use of saline solution is that, as shown elsewhere (see page 1367), it enhances the activity of the autoprotective process while facilitating the renal elimination of toxins or the end-products.

The treatment of acute thyroiditis likewise includes the use of the above measures besides the remedies the causative disease warrants. One feature of importance in this connection is that a high blood-pressure is a pernicious feature of the disorders; vascular depressants, such as chloral hydrate and veratrum viride, preferably the former, therefore, are of considerable value. J. C. Wilson has shown that chloral hydrate can be used advantageously to reduce the peripheral congestion and general distress in scarlatina. As this and other exanthemata are relatively frequent causes of acute thyroiditis, it may safely be employed to counteract this condition.

Surgical measures often become necessary. According to Kocher[21]: "The presence of pus is difficult to demonstrate and premature incision must be avoided. If necessary, the gland itself should be exposed. If incision of the abscess is not followed by rapid recovery, the presence of multiple abscesses should be suspected. Fistula points to extensive necrosis. In such a case the affected half of the gland must be excised. Partial thyroidectomy may also be considered in cases of thyroiditis that have become chronic and in chemicotoxic thyroiditis." In the chronic thyroiditis attended by hypothyroidia, thyroid gland should be given, and the actually diseased part removed surgically, especially if dyspnœa is present.

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[21] Kocher: Keen's "Surgery," vol. iii, p. 380, 1908.

CHAPTER V.

DISEASES OF THE THYROPARATHYROID APPARATUS (*Continued*).

DISORDERS DUE TO EXCESSIVE ACTIVITY OF THE THYROPARATHYROID APPARATUS.

OVERACTIVITY of the thyroparathyroid apparatus, in keeping with the opposite state, described in the preceding chapter, has been identified by numerous terms, the most used of which are pseudo-Graves's disease, aberrant or larval exophthalmic goiter, incomplete Basedow's disease, forme fruste de la maladie de Basedow, hyperthyroidism, and thyroidism. The first five of these were based upon the fact that all of the phenomena were reproduced in exophthalmic goiter, of which the disorder is, in truth, a mild type. The absence of the major symptoms: exophthalmus and goiter, however, so readily misleads the clinician into erroneous diagnoses that the tendency of modern observers is to distinguish this milder type from true exophthalmic goiter, *i.e.*, to regard it as an autonomous syndrome, in which the cardinal symptoms mentioned above are not suggested. Hence the terms "hyperthyroidism" and "thyroidism." As stated in the preceding chapters, however, the terminal "ism" appears to me to suggest the presence of a habit rather than a morbid process subject to treatment. I prefer the term "hyperthyroidia," therefore, which, besides covering this feature, harmonizes with the terminals previously used. To simplify the term, it is not made to include the parathyroids, though, as in hypothyroidia, it must be understood that these glandules are deemed functionally associated with the thyroid proper in the process to be described.

HYPERTHYROIDIA.

(Pseudo-Graves's Disease; "aberrant" or "larval" Exophthalmic Goiter; forme fruste de la Maladie de Basedow; Incomplete Basedow's Disease; Hyperthyroidism; Thyroidism.)

By the above term is meant the aggregate of symptoms which excessive activity of the thyroparathyroid apparatus awakens when the cardinal symptoms of exophthalmic goiter, *i.e.*, exophthalmus and goiter, are missing. There are still, particularly in Europe, a few observers who deny that exophthalmic goiter is due to excessive activity of the thyroid. But their opinion is based only on a few experimental facts which do not stand close scrutiny. Clinical medicine and surgery, on the other hand, backed up by many expermental data,, plead overwhelmingly, however, in the opposite direction. "The whole structure of the surgical treatment of Graves's disease," writes A. E. Elliott,[1] "rests upon the theory of hyperthyroidism, and, if it be not true, then the hundreds of thyroidectomies which are now matters of record remain without justification. The striking influence over the disease, which follows a well-executed partial thyroidectomy, furnishes evidence in favor of the theory of hyperthyroidism, which is so direct as to be apparently irrefutable. The results of thyroid feeding supply evidence which is hardly less conclusive. The administration of thyroid gland substance, or thyroid extract, is capable, if given in sufficient amount, of inducing a toxic state which in almost every essential is similar to Graves's disease." That it can thus be caused both in man and in the lower animals, has been observed by Notthaft, Edmunds, and others. "An artificial state of hyperthyroidism is thereby produced," also writes Elliott, "which duplicates almost in full the morbid syndrome. Even the characteristic exophthalmic symptoms have been observed after thyroid feeding by Auld, Béclère, and others, and Edmunds was able to induce proptosis, widening of the palpebral fissure, and dilatation of the pupils in six monkeys by this means, even after excision of a portion of the cervical sympathetic." That it is the iodine of the thyroiodase which produces it, is also shown by the statement of Kocher that excessive iodide treatment is responsible for the development of exophthalmic goiter in more cases than is generally recognized, the form produced being a severe one.

As to the manner in which such marked phenomena as those witnessed in hyperthyroidia and its aggravated form, exophthalmic goiter, by an excess of thyroid secretion, it must be frankly stated that the existing confusion is eliminated when the functions of the thyroparathyroid apparatus are interpreted, in keeping with the conclusions submitted in the third chapter, (1) that the thyroiodase sustains oxidation and both phases of metabolism—anabolism and catabolism—by sensitizing or increasing the inflammability of the phosphorus of all tissues—including the adrenals and their center and nerves—to the action of adrenoxidase, and (2) that it participates through this same sensitizing action upon all wastes and other eliminable refuse materials in the blood and scavenger cells, in the auto-protective functions of the body, both in health and disease. These two functions once thoroughly apprehended, we shall find that the clinical history of these cases is not difficult to understand. It is perhaps unnecessary to state that the symptomatology of hyperthyroidia illustrates only the phenomena due to exaggeration of metabolism, and that the increased immunizing activity which it entails gives rise to no individual phenomena.

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[1] Elliott: Amer. Jour. Med. Sci., Sept., 1907.

While, as conceded above, there is ground for the recognition of hyperthyroidia as a separate syndrome, the fact remains that its etiology, pathology, symptomatology, and medicinal treatment are practically the same as those that obtain in exophthalmic goiter. It is unnecessary, therefore, to treat the former under a separate head, the reader being requested to look upon hypothyroidia as less severe symptomatically than true exophthalmic goiter, and as presenting neither its two cardinal signs: exophthalmus and goiter, nor its progressive lethal trend, unless, as is often the case, it lapses into this severe form.

EXOPHTHALMIC GOITER.

(Parry's Disease; Graves's Disease; Basedow's Disease.)

Referring to this disease, in the earlier editions of this work,[8] I advanced the view that it was in conjunction with the adrenals that the overactive thyroid gland provoked what I regarded as the *sthenic or first stage* of the disease, my conclusion to this effect being: "Exophthalmic goiter is due to overactivity of the thyroid and adrenal glands, and to the exaggerated tissue oxidation this entails." We have seen that the labors of Kraus and Friedenthal, Kostlivy, and Hoskins have sustained this view. I also concluded at the time, that the stage of the disease (not always reached because of recovery or death) which simulates myxœdema entailed also adrenal insufficiency, the conclusion submitted being: "The *asthenic* or *second stage* of exophthalmic goiter is due to exhaustion and functional insufficiency of the thyroid and adrenal glands, as a result of their prolonged overactivity during the sthenic stage." Here we have familiar clinical facts besides those of myxœdema, to sustain my position. Thus, referring to a case in which the skin had assumed "a peculiar bronze color," W. Macphan Semple[3] expressed the opinion that there might "possibly be some more intimate connection between Graves's disease and Addison's disease than has been so far acknowledged"; Hirschlaff[4] also reported a case due to fright in a girl, in which "there was extensive brownish pigmentation"; von Schrötter[5] likewise observed a case in which "patches of dark-brown pigmentation were found over the entire body." In truth, we are dealing with a not-infrequent symptom of the disease, and recognized as such by classics, which clearly points to involvement of the adrenals.

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[8] Sajous: "Internal Secretions," etc., vol. i, p. 164, 1903.

We must not, however, as has been done, construe this as meaning that I "consider Graves's disease to be the result of excessive suprarenal activity, while myxœdema is due to the opposite condition, adrenal insufficiency." My position is specified in the two conclusions quoted above. Were the adrenals alone active in Graves's disease, its symptoms could not be distinguished from those evoked by adrenal overactivity, treated in the preceding chapter. Acting conjointly with the thyroid, however, the latter introduces factors that are directly traceable to it: the marked emaciation, for example, due to the rapid consumption of the body fat in this disease, as well as in certain adipose subjects treated with thyroid. I have pointed out the influence of the adrenals on oxidation. Now Magnus Levy, Salomon and also Steyrer found that the respiratory exchanges were increased from 50 to 80 per cent.[5a] in Graves's disease.

Yet this does not mean that the influence of either organ may not predominate in proportion as its *relative* efficiency is superior. Thus, Washburn,[6] in a test of my contention that the adrenals take part in the process, writes: "Then we should expect high blood-pressure during a considerable part of the clinical course, that is, during the period of adrenal overactivity," and he gives 160, 170, 160, and 200 mm. Hg observed by him in four cases as proof of the correctness of my postulate. While this is perfectly true, and, as observed by Spiethoff,[7] Morris and Edmunds,[8] and others, there is a tendency toward a moderate rise of blood-pressure, the fact remains that in severe or advanced cases, contrary to what we should expect under the influence of a marked excess of adrenal secretion in the blood, there is a remarkable dilatation of the arteries of the entire organism with pulsation in the liver, spleen, capillaries, etc. Why should this occur? As we shall see, this is due to the action of the thyroid secretion, which, exaggerated, offsets that of the adrenal secretion.

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[3] Semple: Bristol Medico-Chirurgical Journal, June, 1898.
[4] Hirschlaff: Zeit. f. klin. Med., Bd. xxxvi, H. 3-4, 1899.
[5] Von Schrötter: Medizinische Klinik, April 5, 1905.
[5a] Biedl: "Internal Secretory Organs," p. 96, 1912.

And it is between the thyroid and the adrenals that the symptomatology finds its elements. The exaggerated secretory activity of both organs being synchronous, we have merely a correspondingly exaggerated expression of their normal functions. Thus, if the thyroid functions exceed those of the adrenals, we have vasodilation and a more or less marked depression of the blood-pressure; while if the adrenals predominate there is a rise of blood-pressure such as that observed by Washburn. The presence in the blood of an excess of adrenalin, in fact, has, since I urged the participation of the adrenals in Graves's disease, been demonstrated by Kraus and Friedenthal,[8a] and also by A. Fraenkel.[8b]

When fully developed, however, it appears to me that:—

Exophthalmic goiter is a constitutional disease due to excessive functional activity of the thyroparathyroid apparatus, and to the resulting dilatation of all arteries which the excess of thyroparathyroid secretion causes by producing excessive phosphorus oxidation (and elimination as P_2O_5) in all tissues, including the vascular muscles and the depressor nerve.

PATHOGENESIS AND SYMPTOMATOLOGY.—As recently stated by Biedl[8c] "Graves's disease is the direct outcome of the flooding of the organism with thyroid substances." But from my viewpoint, the clinical and therapeutic sides of the question render it advantageous to recognize three stages: 1, the *sthenic* or *erethic* stage, during which the overactive thyroparathyroid apparatus causes excessive sensitization of the phosphorus of all tissues to oxidation, and, therefore, abnormally active cellular metabolism; 2, the *transitional* stage, during which the overworked thyroid is beginning to be restrained by the gradual formation of sclerotic areas and atrophy and, 3, the *asthenic* or *myxœdematous* stage, during which progressive fibrosis and atrophy increasingly inhibit the functions of the organ and finally cause the patient's death. The general vasodilation, though an important feature of the process, is incidental, and, as previously stated, subject to fluctuations.

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[6] Washburn: Wisconsin Medical Journal, March, 1907.
[7] Spiethoff: Zentralblatt f. innere Med., Bd. xxiii, S. 849, 1902.
[8] Morris and Edmunds: Medical News, vol. lxxxvi, p. 62, 1905.
[8a] Kraus and Friedenthal, Berliner klin. Wochen., S. 1709, 1908.
[8b] A. Fraenkel: Archiv f. exp. Path. u. Pharm., June, 1909.
[8c] Biedl: "Internal Secretory Organs," p. 102, 1913.

STHENIC OR FIRST STAGE.—Under "hyperthyroidia" we have seen how clearly the excess of thyroiodase enhances all cellular activities—driving the cell to death, as it were. That the thyroid secretion and extracts increase tissue oxidation is generally recognized, but unlike the oxidation produced by an excess of adrenal secretion or extract there occurs, under the influence of the thyroid secretion, phosphoric acid metabolism and excretion, upon which Chittenden[9] had laid stress. This is a feature of the action of thyroid products upon all phosphorus-containing structures, which stand out even more prominently in the clinical history of exophthalmic goiter than in the milder hyperthyroidia. The brain and nervous system are especially rich, as well known, in this element. The influence of the excessive thyroid activity, therefore, is shown by the greater agitation, restlessness (children being unusually irritable), hallucinations of sight and hearing, capriciousness or unusual gayety in the sthenic stage, which not infrequently includes also pseudo-hysteria, delirium, and even mania. Nervous disorders are so evident in the disease that the latter has been considered by many excellent authorities, including Putnam, as a neurosis. Tremors, especially marked in the upper extremities, but not infrequently involving even the muscles of the back and of the whole body—felt, as indicated by Maude, by placing the hands on the patient's shoulders while he is standing—are practically ubiquitous in these cases. Even the voice may become strident and tremulous. Choreic movements (which may replace tremors in children), local cramps, muscular spasms, and even epileptic convulsions are classic, and by no means rare, symptoms of the disease. They denote undue erethism in the cerebrospinal axis and the peripheral nerves, and explain the excessive excretion of P_2O_5. The undue carbohydrate metabolism noted by Kraus, Ludwig, Chvostek, and others are but additional expressions of the same factor.

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[9] Chittenden: Trans. Cong. Amer. Phys. and Surg., vol. iv, p. 87, 1897.

We cannot ascribe to the thyroid secretion *per se* any more than to the thyroid preparations in common use the powerful oxidizing power this denotes. It is here that "oxidizing ferment" of the blood, *i.e.*, the adrenal secretion converted into adrenoxidase, comes into play. Indeed, concomitantly, we find the evidences of increased oxidation. While a rise of temperature to 100° or 101° is the rule, some cases show a tendency to an acute febrile state, as observed by Gilman Thompson in a series of 70 cases, the fever reaching 104° F. and continuing sometimes several weeks, and recurring every now and then. Few diseases, in fact, furnish examples of such temperatures. In a case observed by Rendu,[10] it reached in the course of one of these exacerbations 110° F., remaining two days between 107° and 110° F. The patients often complain bitterly of a sensation of warmth, of "burning flushes," especially when pruritus and sweating, both due to excessive metabolism in the skin and sweat-glands, are present. The increased demand for food and fluids betokens the intense rate of metabolism to which the tissues are subjected; indeed, polydipsia and boulimia are common. Yet, emaciation proceeds; the thyroiodase, by increasing the vulnerability of the nucleus—also rich in phosphorus—of all fat cells to oxidation by the adrenoxidase, finally consumes all reserve fats; then follow nitrogenous tissues, whose cell nuclei are likewise rich in phosphorus.

The vascular phenomena, referred to above, and others they entail, are due, as stated in my definition, to this excessive oxidation and breaking down of all organic phosphorus, including that of vascular and nerve cells, and particularly Ludwig and Cyon's depressor nerve, which, as is well known, causes general vasodilation and a fall of the blood-pressure. Cyon found, moreover,

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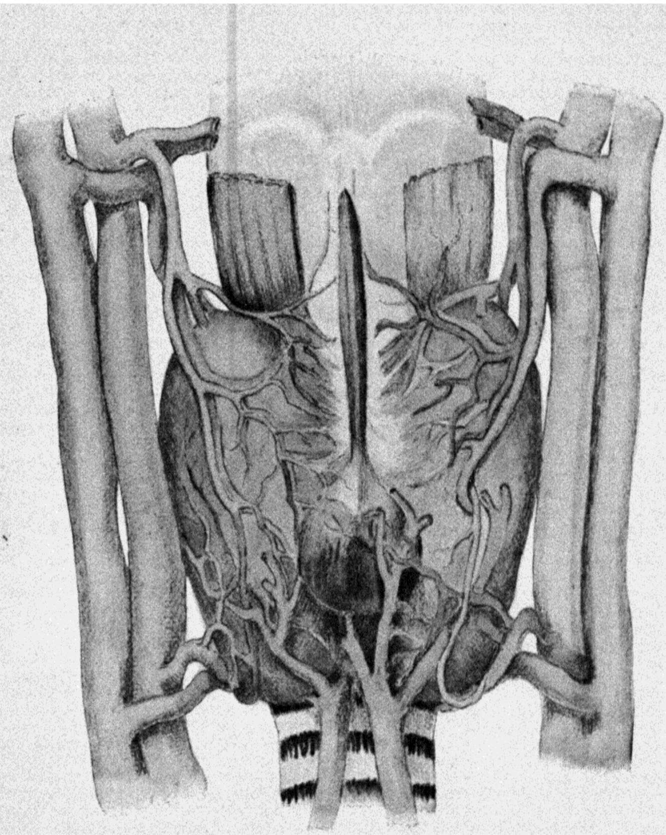
[10] Rendu: Lyon médical, March 11, 1900.



VASCULAR SUPPLY OF THE THYROID GLAND.

that thyroid extracts excite the depressor nerve, an effect which the action of thyroid on the phosphorus of all cells explains.

The vascular dilatation may affect all the arteries of the body and be sufficiently marked to cause pulsation of all the large arterial trunks, most marked at the carotids and transmitted to the capillary system. It explains many, now obscure, phenomena that attend the disease. The tendency to hæmorrhages in the mucous membranes and skin is doubtless due to the fact that the dilated arterioles admit blood into the capillaries in excess of the volume the venules can readily carry off. Hence, the flushing of the skin, the hæmorrhagic areas in the mucous membranes, the epistaxis, the coffee-ground emesis, the subcutaneous extravasations of blood which, as in Popoff's case,[11] may attain huge dimensions, the telangiectasis, and, indeed, the gangrene occasionally witnessed. To the vasodilation may also be ascribed the œdemas often observed in the eyelids and legs, the fugitive swellings of the face, neck, arms, and joints, none of which are, of course, beneficially influenced by thyroid treatment. A distinct "whirr" may be heard in some cases over large vessels, as a result of the unusual volume of blood circulating through them.

The thyroid is, as a rule, only moderately enlarged, and its greatly dilated vessels likewise give rise to a distinct whirr under auscultation, while palpation elicits a thrill. During the first stage the goiter is relatively soft, and yields under pressure.

Exophthalmos, commonly the first sign (sometimes unilateral), belongs, when not merely-apparent, *i.e.*, due to retraction of the eye-lids, to the same vasodilation of depressor origin, the vessels behind the eye-ball, especially of the retro-bulbar venous plexus, becoming greatly engorged. Here also we have dilatation of the arterioles, which admits an excess of blood into the tissues drained by this venous plexus. At first the exophthalmos fluctuates with the vascular dilatation, and may even be caused to disappear temporarily by pushing gently on the eye-balls. Later, no recession occurs owing to the local deposition of fat and connective tissue.

Stellwag's sign (in reality Dalrymple's,[12] who described it twenty years earlier), retraction of the lids, also finds its explanation in this vascular dilatation: the palpebral muscle receiving an excess of arterial blood, it is unduly spastic, in keeping with other muscles of the body. This applies also to Graefe's sign: lagging of the upper lid when the eye-ball moves downward; its muscle being spastic, it cannot carry on its movements physiologically, that is to say, synchronously with those of the eye-ball. This spastic state may, in fact, be discerned by means of L. Napoleon Boston's sign[13]: The head being firmly braced, the patient is directed to follow as high as possible with his eyes the operator's hand, raised upward, starting from the level of the patient's chin about three feet away from his face, then brought down again. The upper lid will be noticed to follow the pupil downward a short distance, then to stop, when what the author terms a "spasm" occurs before it resumes its downward course. The dependence of both Stellwag's and von Graefe's signs upon so fluctuating a factor as the circulation is shown by the fact that they may vary from day to day and that they are not constant.

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[11] Popoff: Neurol. Centralblatt, April 15, 1900.
[12] Dalrymple: London Lancet, May 26, 1849.

The tachycardia, one of the cardinal signs of the disease, in the light of these facts, is an expression of the febrile process, but only in part, for it persists even when the temperature is practically normal. The erethism of the central nervous system and of the nerves themselves, including the accelerator nerve, provoked by excessive oxidation in them, being taken into account, however, the abnormal pulse-rate finds its normal explanation even without the presence of a febrile state. Especially must this be the case in view of the fact that the myocardium itself is rendered hyperexcitable by the blood overladen with thyroiodase and adrenoxidase it receives. The cardiac symptoms of the disease, extreme irritability, distressing violent palpitations, with loud valvular sounds, especially marked at night, and even endocarditis, betoken the presence of such a condition of the entire cardiac mechanism. In children, in whom the disease develops rapidly, as a rule, the cardiac signs are often the first to appear.

The respiratory phenomena are closely allied to the cardiac, in that the respiratory muscles, including the diaphragm, are also rendered supersensitive by the excessive oxidation to which they are subjected by the blood, and the irritability of the nerves:

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[13] Boston: New York Medical Journal, August 17, 1907.

the phrenic, the respiratory nerve of Bell, the vagus, etc., they receive. The chest muscles being cramped, their excursions are restricted, and the air intake is correspondingly reduced. That the bronchial muscles are likewise contracted, abnormally reducing the caliber of the air channels, is probable. These two sources of diminished respiratory capacity suffice, it seems to me, to explain the sensations of suffocation or dyspnœa so often observed in these cases. As is the case with the tachycardia, this dyspnœa is subject to crises, during which the respirations become extremely rapid, sixty a minute, sometimes, as observed in two cases by Sharp.[14] This observer noted that "opium had a marvelous action in slowing the respirations." As shown in the second volume, page 1272 of this work, opium, from my viewpoint, produces its effects by causing constriction of the arterioles—thus opposing precisely the muscular hyperæmia to which I ascribe the abnormal effects.

The alimentary canal is morbidly influenced by the same process, congestion and irritability of the gastric mucosa and muscular coat predisposing to emesis. A similar condition of the intestine is the underlying cause of diarrhœa. The liver, spleen, and lymph-glands are often found enlarged. The hyperæmia of all organs moreover gives rise to a general *malaise* or sensation of discomfort, the sensory terminals of all nerves being rendered irritable.

Various complications may occur, most distressing of which is ulceration of the cornea and loss of vision, through loss of protection of the lids and imperfect lachrymation and lubrication of the ocular surface.

Some cases of exophthalmic goiter recover spontaneously, though very gradually; others suddenly enter into a rapid downward course, which W. G. Thompson has compared to malignant endocarditis, for which disease it is frequently taken. A very rapid, tumultuous, and irregular heart action; hyperpyrexia; dyspnœa with labored breathing; vomiting; diarrhœa; hæmorrhages and ecchymoses; marked congestion and enlargement of the liver; delirium; stupor, and coma. In most cases, however, the typical symptoms of hyperthyroidia are replaced by a period of apparent quiescence—the transition stage—and then lapse into those of hypothyroidia, the normal terminal morbid process of progressive exophthalmic goiter.

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[14] Sharp: London Lancet, June 27, 1903.

Transition Stage.—What appears to me to be entitled to this designation is a period in the course of the disease when there occurs apparently considerable improvement. The skin ceases to be abnormally moist, the heat flushes, the sensation of heat and the fever disappear, and the skin loses its suffused appearance, and may even become pale. The tremors and nervous irritability, and even the mental aberrations and emotionalism, are replaced by a gratifying placidity; the tachycardia greatly lessens, though reawakened by exertion. The emaciation tends also to disappear, and the patient, though weak, may even show a tendency to corpulence. On the whole, he appears to his surroundings greatly improved and even on a fair way to recovery.

If the goiter be examined with due care at this time, it will be found, at least in most instances, to have receded, and to have lost somewhat of its rounded shape. Its former softness still remains in some places, but in others nodular masses or bosses can readily be detected by passing a finger over the mass, and exerting slight pressure. The meaning of this is self-evident: the goiter is undergoing atrophy owing to the sclerotic areas with which it is now studded, and the transition stage is that period of the process during which the normal tissues, *i.e.*, what remains of them, are just able to sustain the metabolic equilibrium—although the latter is further compromised by the deficiency of cellular phosphorus following its excessive oxidation. The time finally arrives when the thyroid secretion produced is no longer sufficient and the case then enters into the:—

Asthenic or Myxœdematous State.—In this stage, reached, as previously stated, if cure or death does not occur early in the course of the disease, we witness the results of exhaustion of both the thyroid and the adrenals with fibrosis of the former. The recognition of this fact is important, for, while thyroid preparations are very harmful in the first stage, as many reported cases show, they may be useful when myxœdema has appeared. During the transition period the change is so rapid in some cases that certain symptoms of both exophthalmic goiter and myxœdema may occur together, the case lapsing ultimately into myxœdema. In textbooks its symptoms, unrecognized, are promiscuously merged in with those of exophthalmic goiter. In a case witnessed by de Smet,[15] the transition followed premature labor, the goiter alone remaining of the first disease. The exophthalmus may also persist.

The myxœdematous phenomena include most of those reviewed under Myxœdema, *i.e.*, the manifestations of hypothyroidia and hypoadrenia, and, as previously shown, the symptoms of impaired oxidation and metabolism these conditions entail. They are, briefly: hypothermia, sensation of coldness, obesity with a non-pitting, rough, dry skin; suprascapular swellings or pads, loss and coarseness of hair, brittleness and ridging of the nails, predisposition to onychia; various cutaneous disorders, leucoderma, scleroderma, vitiligo, brown pigmentation, etc.; mental torpor, depression, and irritability. There is intense weakness, especially of the legs, with occasionally a tendency to tabes-like paralysis, hemiplegia, or muscular atrophy, which may begin during the sthenic stage. There is a tendency to greater heart weakness and dilatation than in ordinary cases of myxœdema, owing probably to exhaustion of the cardiac muscle during the sthenic stage. If the patient is not carried off by some intercurrent disease, cachexia supervenes with a tendency to fainting spells and heart-failure, the usual cause of death.

ENLARGED THYMUS AS COMPLICATING FACTOR.—The thymus sometimes assumes considerable importance in the pathogenesis, pathology, and prognosis of exophthalmic goiter, and may even assume the leading rôle. Both Halsted[16] and Kocher hold that these cases are exceptional, the former surgeon having met about 20 in a series of 500 cases treated by him; others—von Haberer, for example—deem them more frequent than is generally supposed. The fact remains, however, that the thymus has been found persistent in about 82 per cent. of the cases of exophthalmic goiter examined *post mortem* in subjects in whom death had been due to intercurrent diseases, and that out of 133 recorded patients who had died during or soon after an operation on the thyroid, ligation of arteries, lobectomy, etc., for exophthalmic goiter, Matti[17] found that 76.5 per cent. had an unusually large thymus. According to Capelle the proportion is 95 per cent. Such cases are a source of great anxiety to the attending physician. Death may not only occur suddenly during any of the operative procedures on the thyroid, but several days after the operation or even when the patient is apparently convalescent.

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[15] De Smet: Le bulletin médical, Oct. 24, 1906.
[16] Halsted: Johns Hopkins Med. Bull., Aug., 1914.
[17] Matti: Deut. Zeitsch. f. Chir., Bd. cxvi; Kocher: Festschrift, 1912.

Although Halsted states, and doubtless correctly, that the characteristic features which most of these cases present are great emaciation, dilatation of the heart, sweating, diarrhœa, relatively slight exophthalmus, not excessive tachycardia, small goiter, and frequently a peculiar grayish, bronze-hued skin, my own experience has been that it is difficult to identify these cases through this aggregate of phenomena. The clinical history of many personal and reported cases of exophthalmic goiter shows, in fact, that these symptoms may occur irrespective of any participation of the thymus in the morbid process. Yet the presence of this group of symptoms suggests pointedly thymic influence and the importance of establishing this feature of the pathogenesis on a firm basis, since the presence of a persistent thymus in a case of Graves's disease increases greatly its malignancy, and often calls for surgical intervention.

There are a few symptoms that stand apart from the typical Graves syndrome which facilitate materially the recognition of thymic influence. When the goiter is small and the possibility of pressure symptoms from this source is eliminable, dyspnœa on exertion with a sensation of pressure behind the manubrium is suggestive. It is this symptom which, suddenly aggravated, may end in death, after an operation on the thyroid. The patient may then of a sudden gasp for breath, become cyanotic and violently excited, then lapse into unconsciousness and promptly die. Dysphagia with a sensation of impediment, the patient referring to a "lump" also behind the manubrium, may likewise be complained of. The superficial veins of the chest or neck may appear abnormally dilated and prominent. An X-ray examination and dullness over the thymic area will probably indicate the presence of a persistent thymus, which, firmly wedged behind the hard and resistant manubrium, presses more or less upon the underlying blood-vessels and nerves. It is to this pressure that, from my viewpoint, these symptoms should be ascribed, the anatomical relations being such as to account for them.

An important feature which I have never seen mentioned in this connection, is that the size of the thymus varies greatly with the quantity of food ingested. Thus, what has been considered as atrophy of the organ in infantile marasmus is in reality a contraction of the sponge-like organ, which may readily be produced by starvation. Again, any condition capable of raising the vascular tension may so congest the gland as to increase its volume materially. Hence the temporary aggravation of the dyspnœa, dysphagia, etc., under the influence of exercise, a copious meal, etc. Were all symptoms due to a thymic toxicosis they would be continuous, as are, in fact, some of those enumerated by Halsted,—marked emaciation, dilatation of the heart, sweating, etc.

How is this thymic toxicosis produced? This feature of the problem, which has remained obscure, finds a normal explanation through the interpretation of the functions of the thymus I urged in the present work in 1903. Briefly, as stated in the next chapter when describing the functions of this organ, it supplies, through the agency of its lymphocytes, the *excess of nucleins* which the body, particularly the osseous, nervous, and genital systems, requires during its development and growth —*i.e.*, during infancy, childhood, and adolescence, or later if need be, to construct and sustain the functions of the nuclei of its cells. In other words, as is well known, we are dealing with an organ of temporary usefulness, as far as its maximum activity goes, whose activity should virtually cease at a given time—*i.e.*, when the permanent purveyors of nuclein-producing lymphocytes, the bone-marrow and lymphatic glands, are able fully to carry on their functions. When, however, this permanent function is fully established, and a persistent, or even hyperplasic thymus continues abnormally its functions, we have two *sources of nucleins, one of which, the thymic, is in excess and, therefore, injurious.*

This brings us back to what I deem to be the common cause of exophthalmic goiter, viz., some toxic, of which there are at least several, capable of exciting excessively, and through their centers, the functions of the thyroid and adrenals, in a predisposed or neurotic subject, as will be shown presently under Etiology. The poison here being an excess of nucleins, all tissues are abnormally supplied with these phosphorus-laden bodies. The thyroid and adrenals, which, we have seen, participate in tissue oxidation, being also inordinately stimulated, *excessive metabolism is induced in all tissues.* Hence the marked emaciation, the sweating, the diarrhœa (to facilitate the elimination of tissue-wastes), and the exhausted and therefore dilated heart. The tissues are, as it were, "worked to death," the symptom-complex being such as to make of these patients what Halsted has well termed "dreadful cases."

The experimental and clinical data available sustain the pathogenic relationship between the thymus and exophthalmic goiter. Thus, we have seen that lymphocytosis is a feature of these cases, as pointed out by Kocher; removal of the thymus causes a fall of these small mononuclear leucocytes from 40 per cent. to 25 per cent., then often to normal. The fact that, as shown by Garrè, it is the thymus which so aggravates the disease is demonstrated by the observations of Haberer, that the injection of the juice of thymus gland caused thyrotoxis, and of Bayer, that it brought on the lymphocytosis. Bircher, according to Gebele, has also produced typical exophthalmic goiter symptoms by means of intraperitoneal implantation of fresh hyperplasic thymus. On the whole, it is permissible to conclude that *a persistent and particularly a hyperplasic thymus may cause exophthalmic goiter, or aggravate this disease, by adding to the tissues at large, including the nervous system, an excess of nucleins which, acting as a toxic, excite in those tissues abnormally rapid metabolism. The thyroid and adrenals, themselves overstimulated directly, are, besides, rendered overactive owing to their participation in the defensive functions of the body. In both the transition and asthenic stages the thyroid and adrenals, when exhausted, undergo atrophy.*

I urged, as far back as 1903, that the adrenals should be looked upon as participants in the morbid process of Graves's disease; this applies also to the thymic form of this disorder. Thus, Matti[18] found that in all of 10 cases in which the patients had died during or soon after an operation on the thyroid and thymus was found enlarged *post mortem* the adrenals were noted to be exceptionally small.

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[18] Matti: *Loc. cit.*

ETIOLOGY.—In the first edition of this work (1903)[19] I traced the primary cause of exophthalmic goiter to the pituitary body (the neural lobe), through sympathetic nerve-paths. The following year Salmon[20] also concluded that the pituitary body was the seat of primary irritation, though his explanation of the process differed from mine. Briefly, from my viewpoint, the pituitary body contains the co-ordinating centers of the thyroid and adrenals, and when certain toxics capable of irritating this center, such as the toxic wastes of pregnancy and menopause, various toxins, endotoxins, autotoxins of intestinal origin, etc., occur in the blood during a prolonged period, both these organs are unduly excited, and, their secretions being produced in excessive quantities, the disease is awakened.

That exophthalmic goiter occurs in persons predisposed to it by supersensitiveness of the central nervous system, as in hysterical, epileptic, and other neurotic subjects, is suggested by the frequency with which such disorders proceed or occur with the disease. Robinson[21] and others have even gone so far as to consider it as a form of hysteria. Grandmaison,[22] in a study of 32 cases, found hysteria in 19. Abadie ascribes the disease to irritation of whichever center governs the sympathetic vasodilator branches of the thyroidal vessels. Dana[23] vouchsafed a similar opinion. Von Gräfe, Köber, Charcot, and many other authorities have directed attention to the sympathetic in this connection, while Virchow, Trousseau, von Recklinghausen, and others have found lesions (which, from my viewpoint, need not necessarily occur) of the cervical sympathetic, whose branches supply the thyroid. Now, it is through the sympathetic that Cyon traced nerve-paths from the pituitary (the posterior lobe of which is a sympathetic structure, rich in chromaffin substance) to the thyroid, and, as I show in the second volume (p. 982 *et seq.*), the pituitary contains, in all likelihood, the previously unidentified center of the sympathetic system.

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[19] Sajous: "Internal Secretions," etc., 1st ed., p. 514, 1903, and p. 1861, 1907.
[20] Salmon: Clinique Moderne (or Clinical Med.), Aug. 3, 1904.
[21] Robinson: "Étude sur les syndrome de Graves-Basedow considéré comme manifestation de l'hystérie," Paris, 1899.
[22] Grandmaison: Médecine moderne, July 7, 1897.
[23] Dana: New York Medical Journal, June 14, 1902.

One of the most evident indications of the influence of the waste accumulation on the genesis of the disease is shown in pregnancy. Richardson[24] states that "in southern Italy it has long been the custom for the parent to measure the circumference of the daughter's neck before and after marriage, an increase in size being considered as an evidence of conception." Time has sanctioned this popular custom, various observers having shown that the thyroid becomes temporarily congested and enlarged under the influence of what Audebert[25] terms, in describing a case in which exophthalmic goiter developed during the seventh month: the "usual symptoms of hepatic toxæmia." While exophthalmic goiter occurs rarely, the fact remains that it is but the exaggerated expression of a physiological process. Thus, Lang,[26] in a series of 133 cases of pregnancy, found the thyroid enlarged in 108, the enlargement beginning about the fifth month. The thyroid ceased to increase in volume when thyroid gland was administered, and resumed its growth when the remedy was withdrawn.

That we are dealing with an antitoxic function having for its purpose the destruction of wastes of fœtal and maternal origin, is suggested by the fact that the thyroid gland has long been credited with such a function. We have seen that my view that it increased the opsonic power of the blood has been sustained. Reid Hunt[27] found, moreover, that when mice were fed on small amounts of thyroid they showed marked resistance to poisoning by acetonitrile. The relationship of the pituitary body with the toxæmia of pregnancy is also shown by the observations of Comte,[28] that during pregnancy the pituitary body is also markedly enlarged, a fact confirmed by Launois and Mulon.[29] In a more recent paper Launois[30] reaffirms his former conclusion, stating that the anterior lobe (which, from my viewpoint, receives the toxics that awaken the impulses transmitted by the posterior lobe to the thyroid and adrenals) is, during pregnancy, "in a state of marked hyperactivity."

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[24] Richardson: "The Thyroid and Parathyroid Glands," p. 20, 1905.
[25] Audebert: Annales de gyn. et d'obstétrique, Sept., 1906.
[26] Lang: Zeitsch. f. Geburts. u. Gyn., Bd. xl, S. 34, 1899.
[27] Hunt: Jour. Amer. Med. Assoc., July 20, 1907.
[28] Comte: Thèse de Doctorat; Lausanne, 1898.
[29] Launois and Mulon: Ann. de Gynécol. et d'Obstét., 2d série, vol. 1, p. 2, 1904.
[30] Launois: Thèse de la Faculté des Sciences de Paris, 1904.

Another feature which points to the pathogenic rôle of intoxication is that, as stated by Ord and Mackenzie: "In districts where ordinary goiter prevails, the exophthalmic form is also met with." Grasset observed a similar coincidence in France, and Carter[31] in England. The latter author states, moreover, that, while, in a certain valley in the West Riding, the inhabitants on one side of the river, who drink water from hills to the south, do not suffer from goiter, those on the other side of the river, who drink water from hills to the north, suffer a good deal from this growth. Moreover, it is from the latter, or goiter side, that cases of exophthalmic goiter are derived. This clearly suggests that the exophthalmic form is but a development of simple goiter. Indeed, referring to 3 cases of this "secondary" type, Dean D. Lewis[32] writes: "In all these cases a history of goiter of some years' standing could be elicited. Two of these goiters were of the diffuse, colloid type, and one of the mixed type, partly parenchymatous, partly colloid. So far as I was able to determine, these goiters do not differ, histologically, from the simple colloid or parenchymatous goiter, unassociated with Basedow's symptom-complex." Goiter being due, according to prevailing views, to a telluric poison, its exophthalmic form must likewise be due to such a poison.

The relations between bacterial toxins, endotoxins and autotoxins and the thyroid (with the latter organ considered as the source of one of the antitoxic constituents of the blood) also afford considerable evidence in this connection. Roger and Garnier[33] examined the thyroids of 33 cases which had died from scarlet fever, measles, diphtheria, small-pox, typhoid fever, cerebrospinal meningitis, and septic peritonitis, and found in all congestion and hypertrophy with increased secretion, and in two instances (variola and diphtheria) foci of parenchymatous hæmorrhage. Marine and Lenhart[34] also state that syphilis, typhoid fever, influenza, and articular rheumatism are frequently associated with or followed by thyroid hyperplasia. R. Abrahams[35] reported 3 cases which developed in the course of active syphilis.

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[31] Carter: Edinburgh Medical Journal, Oct., 1899.
[32] Lewis: Surgery, Gynecology, and Obstetrics, Oct., 1906.
[33] Roger and Garnier: La presse médicale, April 19, 1899.
[34] Marine and Lenhart: Archives of Internal Medicine, Nov., 1909.
[35] Abrahams: Philadelphia Medical Journal, Feb. 9, 1901.

Closely associated with this class of causes is that described by W. H. Thomson,[36] *i.e.*, auto-intoxication from the alimentary canal due to imperfect gastro-intestinal digestion of nitrogenous foods. Treatment based on this view, in which meat was banished from the diet, and intestinal antiseptics were used, gave satisfactory results. While this view has been criticised, it is evident that, from my viewpoint, such poisons can, as well as any of the others referred to above, bring about the disease in predisposed subjects, by exciting the thyro-adrenal center, and thus cause an excessive production of thyroiodase and adrenoxidase. In a case reported by Aiken,[37] the disease began under ether anæsthesia and persisted six years.

Excessive and prolonged exertion has also been known to produce the disease. Overwork is a generally recognized factor. Dauscher[38] reported a case which came on after climbing rapidly a steep mountain. Harland observed 2 instances which had appeared suddenly in soldiers who had been in action in the Boer War. Potain[39] called attention to the fact that violent anger, which has formed the starting point of exophthalmic goiter, awakens symptoms quite similar to this disease, procidence of the eye-balls, trembling, violent palpitations, sweating, diarrhœa, psychical disturbances, etc. In all such cases wastes accumulate in the organism more rapidly than they can be hydrolyzed into eliminable products, and the disease is brought about precisely as in all the forms of toxæmia previously reviewed.

Fright and other violent emotions, which are relatively frequent causes of the disease, bring it on through a different, though kindred, process. Darwin and Sir Charles Bell, according to Carter,[40] describe a person in intense terror in the following words: "The heart beats quickly and violently, so that it palpitates or knocks against the ribs; there is trembling of all the muscles of the body; the eyes start forward, and the uncovered and protruding eye-balls are fixed on the object of terror; the skin breaks out into a cold and clammy sweat, and the face and neck are flushed or pallid; the intestines are affected." The resemblance of these phenomena to the symptoms of exophthalmic goiter is obvious. I refer, elsewhere in this volume, to the sympathetic center as the *sensorium commune,* in the sense that it bears the brunt of violent emotions, shocks, etc., as one of the most sensitive of all somatic centers. Now, as Carter correctly says, intense terror is "a condition in which the somatic nervous system is, for the time being, almost paralyzed." Traumatic shock, blows upon the head, etc., may produce the disease in a similar way, the violent concussion to which the sympathetic center is subjected, along with the other cerebral and basal centers, being the cause of the molecular disturbance. Delorme and Leniez,[41] for example, reported 2 cases in officers who had been thrown from their horses and had struck the pavement on their heads. There was in both cerebral concussion, followed two months later in the one, and one month later in the other, by exophthalmic goiter. They report a similar though less severe case in a soldier who had fallen from a roof, striking his head. Dyrenfurth[42] observed 3 cases due to accidents. The morbid effects of emotions, traumatic shock, etc., are attributable to a molecular disturbance of the sympathetic center,—which governs the caliber of the arterioles,—*i.e.,* the thyro-adrenal center.

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[36] Thomson: Medical Record, Jan. 13, 1900.
[37] Aiken: Trans. Amer. Ophthal. Soc., 1897.
[38] Dauscher: Wiener med. Presse, Feb. 17, 1899.
[39] Potain: Revue intern. de méd. et de chir., Oct. 10, 1895.
[40] Carter: Edinburgh Medical Journal, Oct., 1899.

We have seen that poisons, by exciting the sympathetic thyro-adrenal center, so exaggerate the functional activity of the thyroid and adrenals that the characteristic action of an excess of thyroid secretion on phosphorus oxidation manifests itself, viz., general vasodilation. With fright or any violent emotion capable of paralyzing the functions of the same center, we have general relaxation of all arterioles which the sympathetic center governs, the acute symptoms of fear being the expression of a temporary exacerbation of this vasodilation, *including those of the thyroid and adrenals,* and, therefore, an abnormal influx of arterial blood in these organs. This means for them, as shown by Claude Bernard in the salivary gland, a corresponding increase of functional activity. In the majority of such cases the resulting disturbances, though sometimes severe, are either recovered from as soon as the central molecular equilibrium is restored or, if this restoration does not occur, it may manifest itself by other disorders. If, however, heredity happens to predispose the victim of fright, shock, etc., to exophthalmic goiter, this disease is the one which develops; the circulation receiving an excess of thyroid secretion, the oxidation of cellular phosphorus becomes excessive, and the general vasodilation, the *deus ex machina* of the morbid process, is perpetuated.

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[41] Delorme and Leniez: Le bulletin médical, July 20, 1910.
[42] Dyrenfurth: Deutsche med. Woch., Nov. 21, 1912.

The prevailing view that heredity influences greatly the development of the disease is based on a sound foundation. Among the examples may be cited the family referred to by Oesterreicher,[43] in which an hysterical woman's 10 children included 8 cases of exophthalmic goiter. One of these had 4 grandchildren, 3 of which suffered from the disease, while the fourth was hysterical. Hare[44] reported a case in a girl, whose great-grandmother and grandmother suffered from exophthalmic goiter, and whose great-aunt, aunt, and mother suffered from goiter, which increased with each pregnancy in the mother's case. Grober[45] reported 4 cases of exophthalmic goiter in the same family, a brother, two sisters, and a niece. R. G. Curtin[46] collected 40 cases of the disease in 15 families.

TREATMENT.—The great value of thyroid preparations in hypothyroidia suggests that they should prove harmful in the opposite condition, hyperthyroidia, and particularly in its most marked type, exophthalmic goiter. Indeed, many cases on record suggest that such is the case. But, in the light of the views submitted in the foregoing pages, the reason for these untoward effects is plain: they were due to the empirical use of these powerful agents and regardless of the stage of the disease and of dosage.

I have urged that exophthalmic goiter was divisible into three stages: the *erethic,* that during which there is excessive sensitization of the phosphorus of all tissues to oxidation and abnormally rapid cellular metabolism; the *transitional,* during which the overactive thyroid has undergone sufficient fibrosis to produce only such secretion as is needed by the body to carry on its functions, and the *myxœdematous,* during which advancing sclerosis of the gland is increasingly inhibiting its functions until these cease and death occurs. It is apparent that during the erethic stage the use of thyroid could but add fuel to the fire; that in the transitional it might prove useful to arrest the excessive activity of the thyroid, which is inducing sclerosis, by relieving it of part of its work, and finally that in the myxœdematous it should prove invaluable, as it does in myxœdema, as a life-saving measure. An even finer subdivision is necessary, however, one in which the primary cause of the disorder is taken into account, if satisfactory results are to be obtained. During the erethic stage, as a general rule, thyroid and iodine preparations are productive of serious harm. Thus, Lépine[47] reported a case in which the use of iodine in the course of a gynecological operation brought on symptoms of exophthalmic goiter, even though the patient had previously shown no evidences of this disorder. Kempner[48] noted, moreover, that the use of the iodides for arteriosclerosis and other disorders sometimes provoked symptoms of the disease. They enhance inordinately the oxidation of cellular phosphorus in all tissues and increase, thereby, the general vaso-dilation, which, as I have shown, underlies all the major phenomena of the disease. In certain *mild* cases that are clearly due to a toxæmia of ovarian, uterine, or intestinal origin, thyroid is valuable (I have seen it cause complete retrogression of the goiter) in small doses, *i.e.*, 1 grain (0.066 Gm.) of the desiccated gland during each meal, with abstention from meats to decrease the formation of toxic wastes; but where the symptom-complex of the disease is present in its entirety, the aim should be to promote constriction of the arteries, and particularly of the arterioles which control the volume of arterial blood admitted into the organs, including the thyroid itself, the post-orbital vessels, and the cardiac muscle. It is because of this action, in my opinion, that Huchard obtained good results from quinine in large doses and ergot recommended by Huchard, Paulesco, and others. The most efficient method of using these vasoconstrictors is to prescribe a gelatin-coated pill containing the *neutral* hydrobromide of quinine 5 grains and ergotin 1 grain, as suggested by Forchheimer, one pill being taken after each meal. If the patient stands it well, another pill may be added at bedtime. At times a patient is met who cannot take more than two pills a day. He should be told to expect little or no benefit short of a month, and that the treatment must be continued for a long time. Usually, after a week or two the pulse rate becomes slowed, the thyroid reduced in size, and the sweating or tremor lessened. The treatment should be continued until all the symptoms have disappeared, which may be in four months or not for three years. The only unpleasant action of the drug, as a rule, is occasional tinnitus, especially if large doses be given. To prevent unpleasant effects, if such occur, and reduce the erethism of the cerebral centers (those of the pituitary in particular) I also give 20 grains (1.32 Gm.) of sodium bromide on retiring, adding 10 grains (0.66 Gm.) of chloral hydrate if the bromides do not counteract the insomnia. Relapses are not rare, but if taken in hand promptly they soon yield to the same measures.

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[43] Oesterreicher: Cited by Chamberlain: "Maladie de Basedow," p. 12, Paris, 1894.

[44] Hare: Intern. Medical Magazine, April, 1898.

[45] Grober: Medizinische Klinik, Aug. 16, 1908.

[46] Curtin: Trans. Amer. Climatol. Assoc., Sept., 1898.

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[47] Lépine: Revue de médecine, Aug., 1912.
[48] Kempner: Centralbl. f. d. Grenzges. d. Med. u. Chir., July, 1914.

In some highly nervous women, especially those who suffer from pseudo-hysteria, any preparation of quinine seems to increase discomfort. In these, the bromides at night, with chloral if necessary to counteract insomnia, should be supplemented by the use of phenacetin in the daytime, 5 grains (0.33 Gm.), gradually increasing the dose until 10 grains (0.66 Gm.) are taken three times daily. As stated above, the bromide reduces the pathogenic hypersensitiveness of the cerebral centers; the phenacetin maintains this action by causing constriction of the arterioles which supply them with blood—a common action of the coal-tar products (of which phenacetin is the safest), as stated in the second volume.[49]

The favorable effects obtained by Rénon and Delille[50] with pituitary gland are explainable in much the same manner. In doses of 4½ grains (0.3 Gm.) of the whole gland (ox), which they subsequently deemed advisable to increase to 7½ grains (0.5 Gm.) in divided doses daily, they obtained marked improvement. Hallion and Carrion[51] then found experimentally that pituitary extracts "always produced their effects by raising the arterial tension," producing at the same time "an intense vasoconstrictor action upon the thyroid body." Briefly, we have here precisely the physiological action necessary—the vaso-constrictor power of the adrenal component of the pituitary gland superseding the vasodilator action of the thyroid.

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[49] See vol. ii, p. 1283 to 1293.

[50] Rénon and Delille: Bull. gén. de thérap., May 8, 1907.

[51] Hallion and Carrion: Soc. de Thérap., March 13, 1907.

The morbid effects of the excessive oxidation of the phosphorus to which the cellular elements are subjected require attention. The resulting exhaustion of the phosphorus in the muscular layer of the arteries aids powerfully the action of the depressor nerve in keeping the general vasodilation, including that of the thyroidal vessels, thus keeping up the disease. This phosphorus must, therefore, be replaced. Hence the value of sodium phosphate recorded by Kocher, Trachewski, Vetlesen (40 cases), and others of the glycero-phosphate of sodium in 20-grain doses three times daily, noted by M. Allen Starr, and of lecithin in alcoholic solution praised by Berkley of Johns Hopkins.

In not a small proportion of cases, the disease may be traced to streptococcic infection through the tonsils, even though this may not be sufficiently marked to cause acute rheumatism. These organs should be carefully examined in every case, and all crypts be carefully cauterized. If hypertrophy be present tonsillectomy should be performed. In some instances a clear history of acute rheumatism is obtainable, the salicylates, preferably the sodium salt, is very useful and soon counteracts the hyperthyroidia when given in 10-grain (0.66 Gm.) doses three times a day. Pyorrhœa alveolaris may also act as cause. Evans, Middleton and Allen J. Smith[51a] having found, in typically diseased tonsils, the crypts to harbor *Endamœba gingivalis*, gave emetin hydrochloride subcutaneously or intramuscularly, in ⅛- to 1-grain doses, with improvement in some cases.

Enteroclysis given at 108° F. is useful when, after clearing out the intestines by means of an enema, the solution, using a quart at a time, is retained sufficiently long to insure considerable absorption. If this is not the case, hypodermoclysis every other day, regulating the quantity according to the case, is indicated. By increasing markedly the osmotic properties and the viscidity of the blood, its toxicity and its exciting action on the thyro-adrenal center are greatly reduced, and the elimination of the pathogenic poisons is greatly enhanced.

[51a] Evans, Middleton and Smith: Am. Jour. Med. Sc., Feb., 1916.

Thymus gland, which, as I have pointed out, owes its action to the phosphorus-laden nucleins it supplies to the nuclei of the tissue-cells, was found accidentally by Owen to be valuable in exophthalmic goiter. Obviously it is only of value where the thymus is not enlarged. It may either be given in the form of sweetbread as food, ½ to 3 ounces (15 to 90 Gm.) daily, or in tablet form, from one to three 5-grain (0.3 Gm.) tablets being given three times daily during meals. It is also obtainable in the form of powder, which, given in capsules in the same doses, obviates the unpleasant taste. By supplying the nerve-cells their normal nucleins, their degeneration and particularly that of their ganglia, to which Charcot called attention, is materially counteracted. S. Solis-Cohen[52] highly recommends thymus gland, but supplemented by intramuscular injections of pituitrin, beginning with 5 minims (0.3 Gm.) three times daily, then gradually increasing the dose until 20 to 30 minims (1 to 2 c.c.) were administered at a dose.

The causative condition must be carefully sought and, if possible, removed. In cases due to pregnancy, menopause, and inadequate ovarian development, the disorder is mainly due to inability of the thyroparathyroid apparatus to neutralize the increasing tide of wastes the blood contains. The organ is abnormally stimulated, in the sense that its arterioles are widely opened to allow a vastly greater volume of arterial blood than usual to enter it, and it becomes enlarged. Here, thyroid *preparations*, starting with 1 grain (0.066 Gm.) *t. i. d.* of the dried gland, are of great value by compensating for the organ's deficiency. If the toxæmia is of intestinal origin, meats should be banished and free saline purgation—in addition to the measures advocated in the preceding two paragraphs—resorted to. Highly nervous or pseudo-hysteric cases are also helped by the bromide, phenacetin, and saline solution treatment, but rest in these cases and in those due to traumatic shock is of great importance. In fact, it must be borne in mind that exertion increases toxic waste formation, and, therefore, the asset of pathogenic poisons, and that rest is always indicated. In most cases, in fact, absolute rest in bed is a *sine qua non* of success. A high altitude—about 2000 feet—is helpful.

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[52] S. Solis-Cohen: Am. Jour. of the Med. Sc., July, 1912.

Various sera obtained from animals deprived of their thyroid: Ballet and Enriquez's dog serum, Möbius's sheep serum, or "antithyroidin," Rogers and Beebe's serum, obtained from rabbits or sheep inoculated with extracts of exophthalmic goiter, are all of value in that they are all antitoxic substances which aid the blood in neutralizing the pathogenic poisons.

Thyrodectin, the desiccated blood of thyroidectomized animals, has also given satisfaction in some cases, in 5- to 10-grain (0.33 to 0.66 Gm.) doses in capsules three times daily.

During the *transitional* stage the treatment depends entirely upon the progress made by the atrophic process. As a rule, however, signs of myxœdema are already present; in that case thyroid preparations are indicated, as they are during the *myxœdematous* stage. The latter is virtually a case of myxœdema and requires the measures recommended for that disease (*q. v.*). In both these stages, however, there is a marked tendency to cardiac failure, and digitalis or strophanthus are precious adjuvants.

The injection of boiling water into the goiter, first suggested by M. F. Porter[83] has given good results. The local discomfort is slight, and a fleeting headache is sometimes complained of. None of the 20 cases reported by Porter suffered any other untoward phenomena, a fact which indicates that the procedure is a safe one provided due care is taken to avoid the large superficial veins and to inject the water inside the capsule. The skin, after being cleansed, is anesthetized with Schleich's solution "by producing a small wheal at the points where the needle is to be inserted." A large, all-glass, graduated syringe, armed with a long and rather fine needle, is employed. It is boiled in the water used for the injection, over an alcohol lamp or a Bunsen burner. When more than one injection is given at one sitting the syringe proper being handled with long forceps, is reboiled each time, the object being to have the water penetrate the gland when as near the boiling point as possible. "With a long needle different areas may be injected through the same skin puncture by partly withdrawing the needle. In this way both right and left lobes and the isthmus may be injected through one skin puncture made in the center of the neck." The quantity injected by Porter varied from 40 to 230 minims (2.6 to 15.3 Gm.), the largest quantity injected in the course of one treatment being 660 minims (44 Gm.). The immediate effect is destruction of thyroid tissue and colloid, a temporary increase in the size and density of the growth being followed by contraction and subsidence of the general symptoms. O'Day[54] has also reported satisfactory results. Quinine and urea hydrochloride injections are also used (see page 259).

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[83] Porter: Jour. of the Am. Med. Association, July 12, 1913.

X-ray treatment may now be used without risk of burning since the introduction of the Sabouraud pastille method of measuring the ray. Pfahler reported marked improvement in 75 per cent. of his cases. The X-ray is of especial value when the thymus is enlarged, a point which should be carefully determined in every case. The ray should not, however, be employed in young children, the thymus being necessary to their development.

The combined use of X-ray and the static current have been found superior to the X-ray alone by W. Benham Snow.[54a]

When the foregoing resources fail, which is seldom the case, surgical measures may be employed. At the present time the tendency is to resort too freely and unwarrantably to surgery.

SURGICAL TREATMENT.—*Indications.**—In hyperthyroidia, whether or not the syndrome of exophthalmic goiter be actually present, much care is required in the selection of cases for operation, many being poor surgical risks owing to bad general condition, acute symptoms, or signs of degeneration of important organs, in particular the heart. Where acute symptoms are present thyroidectomy should be postponed until they have disappeared. Irregularity and varying tension of the pulse. diarrhea, edema of the hands and feet, sleeplessness, and paroxysms of gastric pain are conditions that render postponement of radical operation for a period advisable.

Where partial thyroidectomy is not feasible for the time being, *e.g.*, in acute exophthalmic goiter uninfluenced by medical treatment or injections of boiling water, ligation of both superior thyroid arteries may be performed with advantage, sometimes at one operation, but more usually in two sittings, at a week's interval. Arterial ligation is considered of particular utility in cases with pronounced thyroid pulsation and a thrill in the superior thyroid arteries. Well-advanced cases can thus be made fair or good surgical risks. Some advise injections of boiling water as a measure secondary to arterial ligation, *i.e.*, where the latter fails.

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[54] O'Day: New York Med. Journal, April 3, 1915.

[54a] Snow: Jour. of Electrother. and Radiology, Jan., 1916.

* This subdivision of the subject was written by the author's son, Dr. Louis T. de M. Sajous.

If the reaction attending the first arterial ligation—usually at left upper pole—is not marked, partial thyroidectomy, consisting in removal of the opposite lobe, the isthmus, and possibly a portion of the same lobe, may be performed a week later; if evidences of shock be pronounced, on the other hand, an interval of several months (four months—Mayo), during which time will have been given for improvement in the patient's general condition, should be allowed to elapse before partial thyroidectomy is resorted to.

In a small proportion of cases a relapse occurs some years after partial thyroidectomy, the residual glandular tissue undergoing hypertrophy and symptoms returning. If medical treatment be not, under these circumstances, soon beneficial, the vessels at the upper pole of the remaining lobe should be ligated, unless this has previously been done, in which case ligation of the inferior thyroid artery is to be advocated. If arterial ligation fails to prove sufficiently effective, a portion of the lobe may be removed. The risk of provoking myxœdematous symptoms if too much tissue is removed should always be borne in mind.

In some already seriously affected patients, preparatory treatment by absolute rest, heart tonics, diuretics, and the X-rays is required even before arterial ligation is permissible. The X-rays have been serviceable in helping exophthalmic cases through acute attacks, previous to operation.

The superior thyroid arteries are generally ligated in preference to the inferior because they are more accessible and less closely related to important nerves and vessels. Ligation of the inferior thyroid, a more difficult and serious procedure, is only infrequently performed. Ligation of all four arteries in a single case is warned against by Kocher, in view of the danger of cachexia strumipriva where there is such a complete interruption in the blood-supply to the gland.

Early cases of exophthalmic goiter, according to Mayo's experience, sometimes show marked improvement under ligation of both superior thyroid arteries. A complete cure may even follow, rendering subsequent partial thyroidectomy unnecessary. In the more severe cases, general health is frequently so improved by ligation that later removal of the larger thyroid lobe can be effected with but little risk. The possibility that too much glandular tissue for purposes of subsequent sufficient thyroid functioning may thus be removed is not denied by Kocher, but resulting symptoms of hypothyroidism are seldom met with.

According to Mayo, the proportion of exophthalmic goiter cases coming under the surgeon's observation in which removal of the larger thyroid lobe and isthmus can be undertaken without undue risk is about two-thirds. The sphygmomanometer, electrocardiography, X-ray examination of the heart, and the blood-count are all factors of value in the selection of an operation suitable for a case in hand.

Simultaneous excision of one lobe and ligation of one or both arteries on the other side have been advised by some surgeons, notably Landströmme and Klemm. Though good results have been reported, the risk of inducing hypothyroidism would seem to be greater in this connection than with procedures ordinarily followed.

In unilateral goiter with hyperthyroidism, three-fifths of the enlargement may be readily removed, after due preparation of the patient by measures calculated to improve the general condition (Bainbridge).

Where goiter with hyperthyroidism recurs after an initial partial thyroidectomy, the production of atrophy of the remaining thyroid lobe through ligation of one or both of its arteries may be attempted. Thyroidectomy for recurrent goiter is generally more difficult than an initial similar operation owing to the presence of adhesions or scar-tissue.

At times in pregnancy hyperthyroidism develops, rapidly or gradually, with a severity sufficient to require prompt surgical intervention. Generally some degree of hyperthyroidia has existed before conception in these cases, and the increase in the severity of the symptoms is noted early in pregnancy. Matlack operated three times in such cases, with good results, the patient's going on safely to term.

Removal of the thymus gland has been advised by some in exophthalmic goiter, in view of the recently ascertained causal relationship of the former organ to the disease. A persistent thymus has been found in about 90 per cent. of all operations for exophthalmic goiter in which the condition of the organ has been investigated (Bainbridge). Good results have already been recorded by many. from thymectomy in exophthalmic goiter cases in which a persistent thymus is found.

Haberer's experience has been that a combined partial operation on both the thyroid and the thymus in these cases yields better results than partial removal of either organ alone. A promising procedure also is the use of the X-rays to reduce the thymus before an operation on the thyroid is undertaken.

Operative Risks and Results.—Even simple and apparently innocuous procedures have been followed, in hyperthyroid cases, by serious symptoms and even death. The chief danger is collapse preceded by extreme tachycardia and nervous excitement. The symptoms witnessed have been ascribed to intoxication with thyroid material or to violent excitation of the local vasomotor and trophic nerves. Death within a few hours or days may follow. Matlack, in a series of 202 operated cases of exophthalmic goiter, had 4 deaths from postoperative hyperthyroidism. Other attendant dangers are tetany, due to removal or crushing of parathyroid tissue, myxœdema, due to excessive removal of thyroid tissue, and injury to the recurrent laryngeal nerves. The author of the present work considers the belief that death is due to thyrotoxis in these cases a grave error and the cause of several deaths. He attributes these results to shock and the temporary arrest of function of the various glands which cooperate with the thyroid, and has saved life by the immediate use of hypodermoclysis and adrenalin, 20 drops of the latter (1:1000 solution) being injected drop by drop into the rubber tube conveying the saline solution to the tissues.

With careful selection of cases, however, as well as painstaking technique, the operative mortality in exophthalmic goiter should be low. Mayo in 1912 was able to report a consecutive series of 278 operated cases of exophthalmic goiter without a death. On the whole, the mortality in this condition has in recent years undergone a marked reduction, not only through earlier operation and technical improvements, but because of more careful preparation of patients, safer anesthesia, and adaptation of the type of operation to conditions in the individual case. The general mortality from operation at present is from 1 to 4 per cent. In advanced cases with marked tachycardia, irregularity of the pulse, pronounced emaciation, and loss of strength, death occasionally takes place in a few days after partial thyroidectomy, even though the operation has been done under local anesthesia, and in the absence of infection of the wound. The author of this work advocates organotherapy, *i.e.,* adrenalin or pituitrin injections with hypodermoclysis as a protective measure. Such risks may also, as already suggested, be avoided by a preliminary arterial ligation. The thyroidectomy may be effected later if, in spite of general symptomatic improvement, evidences of compression of the trachea persist. Arterial ligation is, moreover, so much safer than thyroidectomy that through its performance the surgeon is enabled to accept as surgical risks cases so advanced that there is but little hope of cure.

As regards the results of operation, the recent experience of surgeons has been that either cure or improvement follows operation in a large majority of cases of exophthalmic goiter. Kocher, in a series of 320 cases, obtained a complete cure in 150 and improvement in 148. In the "improved" cases individual symptoms such as exophthalmos and functional disturbances due to the thyroid disorder, had not been removed, though pronounced betterment in the general condition was noted. In the remaining 22 cases the final results were not good, either because of inability to complete the operation, recurrence, or the persistence of renal or hepatic disturbances.

The immediate beneficial effects of operation in exophthalmic goiter may not be maintained, either by reason of recurrence or through transformation of the residual thyroid tissue into a goiter. Symptoms of hyperthyroidism relieved by the operation may thus return after a long or short interval of health.

After partial thyroidectomy the tendency of the remaining lobe and isthmus is to a lessened hyperplasia, but in 6 or 8 per cent. of cases a compensatory hypertrophy takes place instead and causes persistence or exaggeration of the symptoms (Brenizer). On the other hand, myxœdematous symptoms may appear early in some cases. Although one-fourth of the normal amount of thyroid tissue is generally considered sufficient to fulfill, where the necessity arises, the functions of the entire gland. Conversely, signs of myxœdema may be observed even where but a comparatively small amount of the tissue has been resected. Such myxœdema may prove only temporary, the remaining thyroid tissue finally assuming sufficient activity to meet the needs of the organism. Such a serious mistake has, however, been made as to perform an additional thyroidectomy where signs of hypothyroidism—confused with those of persisting hyperthyroidism,—were already present.

In some instances a return of pressure symptoms due to cysts left in the thyroid at the first intervention and subsequently increasing in size demands a second operation.

In the favorable cases, such conditions as tachycardia, palpitation, chronic lung congestion, and edema of one of the arms rapidly disappear when the excessive thyroid action has been corrected. Difficulty in swallowing, where previously present, is likewise soon relieved, though it may be maintained or increase during the first week. Dyspnea rapidly disappears after operation in the great majority of cases. Hoarseness and even a total laryngeal paralysis may be relieved by the operation. In 2 cases reported by Bérard neuralgic disturbances of the upper extremity, with beginning atrophy of the shoulder-muscles, were caused to disappear by partial thyroidectomy.

On the whole, when all the possible complications and drawbacks attending the operative treatment of exophthalmic goiter are taken into account, and the results are compared with those obtained by medical treatment, the latter should invariably be given thorough trial before surgical measures are resorted to.

GOITER.

(Struma; Bronchocele.)

Goiter, an enlargement of the thyroid gland, may be of limited or prolonged duration. It differs from the disease just considered, exophthalmic goiter, in that it does not give rise, in its characteristic form, to systemic symptoms. It is important to bear in mind, however, that goiter is sometimes the precursor of exophthalmic goiter, and that in such cases the routine use of iodine or thyroid gland may initiate the latter far more serious disease. Considerable evidence to this effect was adduced in the preceding article.

ETIOLOGY.—Although goiter in its various forms may be said to exist in all countries, irrespective of race, it shows a predilection for certain countries, Switzerland, France, Austria, Germany, Italy, and certain parts of England and of the United States. This applies also to special districts of these countries; thus, according to Lobenhoffer,[55] some towns of Bavaria show a proportion of 21 to 26 per cent. of cases of goiter; in France, the greatest number of cases are found in the departments bordering on the Alps and the Pyrenees, and in America, in Michigan, and in Ontario, Canada.

As to the topographical characteristics of the countries in which goiter occurs, much prominence has been given to the influence of altitude because Bircher's map indicates a predilection of goiter for the mountainous districts of Middle Europe. That this cause is of secondary importance is shown by its presence in flat countries such as those stretching from the north of Paris toward Belgium, along the valley of the Thames, the low-lying districts of Ontario and Michigan, and in the Chitral and Gilgit of India, where, according to McCarrison,[56] goiter is endemic. In the Philippines, the disease, according to Duncan,[57] is very prevalent in the municipality of Macabebe, which is but a few feet above sea-level on the northeast shore of Manila Bay.

The drinking-water of goiter districts has long been recognized as the intermediary of agents capable of producing it. In such districts families which received and used faithfully water from elsewhere avoided the disease. Certain fountains in the Canton of Berne, Switzerland, were found to produce goiter almost invariably in the children who drank it. The residuum of filtered water derived from such fountains or springs, when added to the usual and harmless water administered to dogs, guinea-pigs, and monkeys, was found by Wilms[18] to cause goiter in these animals. Much evidence is available in literature proving definitely the rôle of water in transmitting the causal agent of the disease.

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[55] Lobenhoffer: Mitteil a. d. Grenzgeb. d. Med. u. Chir., Bd. xxiv, Nu. 2, 1912.
[56] McCarrison: London Lancet, Jan. 25, 1913.
[57] Duncan: American Med., Nov. 18, 1905.

As to the nature of this cause, ample modern evidence has eliminated the idea of a single agent being the common factor in all cases, and shown that goiter could be produced by many different agents, inorganic and organic, acting as poisons. Calcium is a widespread agent of this sort, districts in which the geological formation contains vast quantities of limestone showing a large proportion of goitrous inhabitants—50 per cent., for example, in some of the limestone districts of India. In such districts in England, where goiter is exceedingly common, those inhabitants who use rain-water as sole beverage are, according to Morris, free from the disease. The silicates, magnesia, alum, iron, manganese, copper, lead, and many other minerals have also been incriminated by various investigators.

An abundance of organic matter in drinking-water is increasingly asserting itself as an important cause. This is emphasized by the fact that during the rainy seasons of India, when organic matter is rapidly disseminated, the number of cases among the whites and natives is greatly increased. Kocher has urged the importance of this causal agent in Switzerland. The promiscuous use of human feces in their natural state so common in that country, which stands first in its proportion of goitrous individuals, recalls the experiments of Suzuki, who produced enlargement of the thyroid in rats by feeding them with cooked rice mixed with rat feces, and also by injecting the latter subcutaneously. McCarrison observed a similar result in animals allowed to drink only water polluted with feces.

While the ingestion of organic matter of this class may bring into activity a large number of pathogenic agents it recalls the stress laid on some pathogenic organism or its toxin as an exciting cause of goiter by Poncet, Jaboulay and Rivière, Klebs, Kocher, Lustig and Carle, Waters, and others. Kocher, in fact, found that "goiter water differs from goiter-free water in containing many more micro-organisms." McCarrison has also ably defended the same views, the soil deposits at the bottom and sides of water channels, tanks, wells, etc., contaminating the water used. The participation of calcium in the pathogenic process is explained by the fact that the organism requires a calcareous soil to flourish. It may be conveyed to places where the disease has not hitherto prevailed and, if the conditions are favorable in that location, it can provoke goiter. The feces constitute the probable medium through which the germ, toxin, or virus leaves the body, all evidence pointing to the intestine as intermediary in the process of infection.

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[18] Wilms: Deut. Zeit. f. Chir., Jan., 1910.

My own view is that bacterial infection may also occur through the intermediary of the tonsils; local treatment of these organs when the seat of catarrhal disorders, either general or limited to the crypts, having enhanced materially the beneficial effects of general measures. The entire nasopharyngeal cavity, the lingual tonsil, the teeth and gums—the latter being frequently the seat of pyorrhea alveolaris—and all structures, in fact, through which a continuous process of infection may occur, can thus harbor the pathogenic factor of goiter.

Various organisms of the ameba type have been shown to provoke goiter, doubtless through a toxin or endotoxin produced by them. Waters incriminated an organism resembling the hematozoön of malaria. Grasset also found this parasite in recent cases. Chagas traced cases to the bite of an insect, *Conorrhinus megistus,* and Brumpt to various insects, especially the bedbug, which act as hosts for some pathogenic organism.

Marine[89] found recently that the feeding of liver and heart to trout produced goiter. Reid Hunt obtained a similar result by feeding liver to mice. This recalls that excessively nitrogenous foods were included by Munson in 1895 among the causes of goiter. Baumann also noticed that a flesh diet stimulated the thyroid in dogs to active hyperplasia. This again is due to intoxication by intermediate protein wastes and nucleins. The latter, as I have shown, are the source of the toxemia to which the form of exophthalmic goiter, caused or aggravated by a persistent and hyperplasic thymus, is due.

On the whole it is evident that *goiter may be caused by*

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[89] Marine: Jour. of Exper. Med., Jan. 1, 1914.

various kinds of toxics, organic as well as inorganic, and endogenous as well as exogenous.

Goiter occurs more frequently in females than in males, and in children than in adults. Many instances have been recorded showing that the disease may be hereditary, but this is doubtless due to the fact that the defensive functions against intoxications of various kinds are themselves deficient in many families.

How do the various toxins, individually or severally, bring on the enlargement of the thyroid identified as goiter? This question can only be answered by adopting my personal view that *the thyroid gland—including always its parathyroids—is intimately connected with the autoprotective or immunizing functions of the body.* Goiter being due to intoxication from some poison, organic or inorganic, we are logically led to the conclusion that inasmuch as infections, toxic wastes, etc., cause enlargement of the thyroid, it is because this organ is the seat of a defensive reaction that it becomes enlarged.

While the disease may be the result of prolonged overactivity of the gland, characterized by typical histological lesions of hyperplasia and hypertrophy, with symptoms of hyperthyroidia, these lesions may also occur in a gland which is unable, even under violent stimulation, to react adequately to the poison. Driven, nevertheless, to inordinate activity, it undergoes violent congestion, thus causing the development of a relatively rapid form of the disease. When this identical morbid process develops slowly under the influence of a given toxic, hyperplasia develops as a result of the persistent congestion and what is usually termed a simple or parenchymatous goiter results.

VARIETIES.—Interpreted from my viewpoint, *i.e.*, in the light of the above-described pathogenesis, goiter may be divided into five distinct types: 1, *simple hypothyroid non-toxic goiter* (generally termed simple or parenchymatous goiter), the underlying cause of which is an inherent inability of the thyroid apparatus to produce enough of its secretion to carry on its antitoxic functions beyond those of normal health, any excess of functional activity to meet the needs of an intoxication of endogenous or exogenous origin provoking congestion, hyperplasia and enlargement of the thyroid, *i.e.*, goiter; 2, *hyperthyroid or toxic goiter*, an aggravated form of the simple hypothyroid type due to excessive secretory activity occurring as a result of the congestion and hyperplasia, and provoking the characteristic symptoms of hyperthyroidia, larval, or even frank Graves's disease, though in most cases without exophthalmos; 3, *hypothyroid degenerative goiter*, divisible into several subtypes such as colloid, cystic, fibrous, etc., in which the degenerative changes denoted by these terms occur probably also as complications of the hypothyroid non-toxic goiter; 4, *malignant goiter*, in which the thyroid or accessory thyroid tissues become the seat of carcinomatous, sarcomatous, or other malignant processes; 5, *congenital goiter* or *goiter of the newborn*, which corresponds pathologically in most instances with the congestive or hyperplastic type of adults, and occurs in a large proportion of cases, in the newly born offspring of goitrous parents and as a result of pressure during birth.

SIMPLE HYPOTHYROID NON-TOXIC GOITER.

The etiology submitted in the foregoing pages entails the conclusion that not all thyroid glands (including their parathyroids) are functionally equal. While a normal gland can fulfill its protective function under the stress of any intoxication or infection without undergoing material enlargement or organic change, a gland weakened through hereditary influence or local lesions resulting from focal autolysis or hemorrhages which occur in the course of diphtheria, and other diseases, is unable to stand the stress. Such a gland secreting a deficiency of its normal product, may swell and thus become a "hyposecretion" goiter. The enlargement here is the result of an effort to compensate by overwork for the deficient output of the gland. Such goiters rarely show true hypertrophy; they are mainly the seat of an active hyperemia with an increase of normal cellular elements in their active parenchyma.

The enlargement may be the first symptom noticed, and through, as a rule, undue tightness of collars previously worn without discomfort. As the goiter develops, it remains soft and diffuse, showing perhaps a tendency to grow larger on one side, usually the right.

In a large proportion of cases, casual observation will elicit no general symptoms of hypothyroidia; careful examination, however, will reveal some symptom or other of this condition. The pulse may be slow, ranging from 62 down to 40 or even lower. This bradycardia is witnessed unless some cardiac complication be present. There is a marked tendency to hyperidrosis, especially of the extremities, excessive sweating occurring under slight exertion and sometimes even without it. Hypothermia is habitual, though seldom marked, and there is a tendency to cold feet and hands. The urea excretion may be reduced one-third. There are no pressure phenomena, unless the growth is far advanced—no dyspnea, no dysphagia. Nor are there nervous symptoms such as those that are common to hyperthyroidia and exophthalmic goiter—no tremor, no exophthalmos. There is, however, a tendency to rebellious rheumatic pains, often about the nucha or between the shoulders, especially marked when the patient lies abed and, therefore, relieved by rising.

Although this form of goiter sometimes recedes of its own accord, its tendency is to persist if the cause be not removed, and to undergo colloid, cystic, or other retrogressive changes. It is a pernicious form in the sense that in the child it tends toward the production of cretinism and, in the adult, to the corresponding condition, myxedema.

A careful study of the general symptoms is necessary here to determine the true nature of the goiter. Treated in time and by removal of the cause, if the latter can be located, and with appropriate remedies, these cases usually recover. It is the form of goiter which, as Kocher states, "is not usually brought to the surgeon for treatment because it can be cured by internal medication," *i.e.*, by means of iodine or its preparations. This is readily understood when we recall that iodine supplies that which the thyroid cannot provide, in organic combination, in sufficient quantity. The halogen thus relieves the functional stress which causes the organ to enlarge.

It is very important to differentiate this hypothyroid type from that which is characterized by overactivity of the gland, the hyperthyroid type, and which therefore iodine, thyroid gland, the iodides, etc., only serve to aggravate. In the latter form we find none of the landmarks of the hypothyroid type. Indeed, as soon as any appear other than the goitrous enlargement, they are clearly those of *larval exophthalmic goiter* or hyperthyroidia, the early signs of which are a somewhat rapid pulse, so-called "nervousness," with tremor so slight, perhaps, that it is revealed only on careful examination. As we shall see under "Treatment," however, cardiac disorders other than those due to true hyperthyroidia may attend goiter and not preclude the use of iodine or its congeners.

As to the physical signs, the shape of the gland is not materially changed as this enlarges, at least at first. Any increase in size can only be discerned by palpation, though inspection may elicit a local enlargement during deep respiration, deglutition, and coughing, owing to the up-and-down motion of the gland. A diffuse goiter grows in all directions, the two lobes meeting medially unless the isthmus is also involved, which is often the case. The neighboring muscles are either raised or moved aside, according to their relative position.

The growth also covers the trachea, but this canal is only compressed when one side of the growth becomes much larger than the other, causing dyspnea. This is not severe in simple hypothyroid goiters, as a rule, when the tumor is not hard, and is apt to occur only on exertion. Compression and displacements of the vessels are also rare unless the tumor be very large. We may then witness slight symptoms due to vascular obstruction: headache, vertigo, etc. Murmurs may be heard in the dilated blood-vessels of the neck, the latter usually projecting more or less from the surface while the growth itself may be seen to pulsate.

Pain does not occur in a gotier unless it be the seat of an inflammation, strumitis, which not infrequently occurs in the course of acute febrile diseases, or of a malignant growth. Unless inflamed or the seat of a cancer, the enlarged gland is freely movable.

From exophthalmic goiter, a simple non-toxic goiter is recognized by the absence of any of the systemic symptoms of the former disease, tachycardia, tremors, etc., and of exophthalmos. From the other forms of goiter, colloid, cystic, fibrous, etc., it is distinguished by its diffuse or even surface, all the latter varieties being more or less nodular under palpation, and by its more recent onset.

Examination with the X-rays is indicated to ascertain whether the case be not complicated with an intrathoracic goiter (*vide infra*) or an enlarged thymus.

PATHOLOGY.—The tissues of these non-toxic goiters, in which hypothyroidia prevails, are strikingly devoid of all signs of hyperplasia or hypertrophy, the enlargement being mainly vascular. At the Mayo clinic according to L. B. Wilson[80] less than 1 per cent. of 3563 cases coming for operation for goiter show any considerable primary hypertrophy and hyperplasia of the parenchyma of the thyroid except as associated with clinical symptoms of true exophthalmic goiter. Even mild degrees of hyperthyroidia with slight enlargement, such as occur during pregnancy, showed some signs of hypertrophy or hyperplasia.

PROGNOSIS.—In young subjects and pregnant women, the hypothyroid non-toxic goiter occasionally recedes of its own accord, but as a rule its tendency is to persist and grow, if left untreated. Though apparently benign, it may not be so in the child, since it may initiate cretinism by depriving the body at large of a part of its supply of thyroid secretion; the adult is exposed to myxedema from the same cause. It may also represent the earlier stage of the various forms of nodular goiter, *i.e.*, those which are the seat of colloid, cystic, fibrous or other retrograde changes. Properly treated, however, before these complications have occurred, these goiters readily yield.

TREATMENT.—Elimination of the cause sometimes suffices to produce retrocession of the goiter. When it is endemic, the toxic is probably a water-borne one, mineral or organic. We have seen that the former include calcium as a frequent cause, and the latter pathogenic organisms, fecal pollution and other contaminating agents. A change of water used for drinking and cooking purposes is therefore an important feature of the treatment. The diet should also be controlled since a free use of meats has been found by Waters, Baumann and others to promote the growth of goiter; liver we have seen actually causes goiter in trout and mice. A meat-free diet, or at least the omission of red meats from the food, is very helpful in most cases by reducing the proportion of nucleins which activate abnormally as poisons the inadequate thyroid and cause it to become hyperemic and enlarged.

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[80] L. B. Wilson: Jour. of the Am. Med. Assoc., Jan. 10, 1914.

Autointoxication of intestinal origin is an important factor. A rich diet may also act as an indirect cause of goiter, as urged by Waters, Baumann and others. A meat-free diet sometimes suffices to reduce the size of a goiter. The purpose here is to prevent autointoxication mainly by nucleins, and thus reduce the work of the thyroid as a factor in the defensive functions of the body.

To attain the same object purgatives are indicated wherever the intestinal action is not free. It should be maintained by means of saline aperients, preferably the sodium phosphate 2 drams (8 Gm.) daily, and if any autointoxication of intestinal origin is discernible, or if pathogenic organisms, entozoa in the alimentary tract, be a possible cause, intestinal antiseptics, thymol, the sulphocarbolate of zinc, betanaphthol, sodium salicylate or creosote carbonate should be administered. Messerli[61] advocates, on the basis of excellent results, continuous mild purgation to keep the intestinal bacterial flora down as much as possible.

A purulent focus in any organ may also provoke the thyroid overactivity which maintains, or leads to, goiter. Catarrhal disorders of the nasal cavities, including the sinuses and vault, the ears, lingual tonsil and the gums, especially pyorrhea alveolaris, should, therefore, be recognized as causes and treated with due thoroughness. The most prolific etiological factors of this nature, however, are conditions of the tonsils which in any way tend to favor the accumulation of bacteria in the crypts of these structures or behind them. Extirpation of these organs, besides being sometimes dangerous in these cases owing to the dilatation and engorgement of the neighboring vascular channels, does not afford the best results. Each purulent focus should be carefully cleansed, then cauterized with either galvanocautery or ignipuncture. Less active measures do not procure lasting results. Adenoid vegetations may also cause goiter in the young by perpetuating an autotoxic process. Coble,[62] for instance, obtained complete disappearance of a goiter in a boy of 15 years, by removing an unexpectedly large adenoid. Pelvic disorders in which ulceration is present should also be remedied.

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[61] Messerli: Revue Médicale de la Suisse Romande, March 19, 1915.

[62] Coble: Indianapolis Med. Jour., Feb., 1909.

As regards internal medication it is only, as previously stated, in these hypothyroid cases that we may with certainty expect results from iodine and its preparations or from its organic congener—that contained in thyroid gland. As advised by Kocher, however, and as my own experience has shown, iodine and thyroid gland should be reserved for the cases that are free from pressure symptoms—remembering always, however, that hysterical cases often experience a sensation of choking irrespective of the goiter—and where the growth has been growing slowly. Its mode of action suggests itself in the light of my views: it enhances directly or indirectly the antitoxic function of the thyroid apparatus, by enhancing its activity or of its secretion in the blood-stream, and thus aids in breaking down the toxic which causes the goiter. The sodium salt of iodine, sodium iodide, is to be preferred to the potassium salt, the ion of which may affect the heart unpleasantly. A dose of 5 grains (0.3 Gm.) three times a day, given immediately after a meal in a small tumblerful of water, will awaken no gastric disorder, even when gradually increased to 10 grains (0.6 Gm.) taken in the same manner. Some cases respond better to the action of Lugol's solution; 3 to 5 drops may be given in the same way as the iodide salt.

The patient should be watched carefully and, if any sign of iodism appears, the use of the iodine salt should be discontinued a few days, after which it may be resumed by starting with a smaller dose—just enough to approximate iodism without provoking it. To arrest iodism, if it should persist, Fowler's solution in 2- to 3- minim (0.12 to 0.18 Gm.) doses in half-glassful of water after meals, sometimes proves effective. But its administration should be discontinued as soon as the untoward symptoms disappear.

Steadily as the enlarged gland is aided by the halogen in carrying its antitoxic functions, it recedes if the goiter be an hypothyroid (parenchymatous) growth, and if the sources of the causative intoxication have been thoroughly eradicated.

To activate the action of the iodine salt, a 5 to 10 per cent.

ointment of iodopetrogen (U. S. Formulary) should be rubbed into the gland daily, ceasing as soon as iodism or irritation of the skin appears. A piece the size of a small hazelnut suffices if properly rubbed in. Its application should be preceded by a period of massage of ten minutes' duration, the movements being directed downward and outward and synchronous with deep inspirations. This and the compression exerted cause a reflex contraction of the vascular channels, and hasten materially the curative process. Where iodism tends to appear, the ointment of biniodide of mercury weakened by the addition of an equal quantity of simple ointment should be used instead. If irritation of the skin is produced the intervals between the applications should be prolonged.

Formerly, iodine, iodoform and other drugs were injected into the growth. But this method has been generally abandoned owing to its dangers, death having resulted in a number of instances. Moreover, its indications being the follicular or parenchymatous type—our hypothyroid form—it affords no advantage over the internal use of iodine or its congeners.

As previously stated, any sign of hyperthyroidia or larval exophthalmic goiter precludes the use of iodine or thyroid, or any preparation of the agents; yet care is necessary to avoid attributing to hyperthyroidia symptoms which may suggest the presence of this condition and yet be due to hypothyroidia. The organ which most frequently misleads the clinician in this connection is the heart, owing to the frequency with which this organ is the seat of organic lesions. Thus, in a study of 381 cases of goiter and of the autopsy records of 720 cases, Shranz found organic lesions of the heart, irrespective of valvular lesions, in 23 per cent. of goitrous children and 49 per cent. of goitrous adults. The morbid process found to predominate in the autopsy records, 25 per cent. of all subjects examined, proved to be degeneration of the myocardium—a condition clearly explained by the participation of the thyroid secretion in tissue metabolism which I advocate. Deficient thyroid activity thus means defective cardiac nutrition, in keeping with the corresponding condition of the rest of the body when the hypothyroidia has existed sufficiently long. Dilatation of the right ventricle (Rose's goiter heart) is a form of disorder not infrequently met with, and which gives rise to pulmonary congestion—Kocher's pneumonic goiter heart. Conversely we may encounter a condition in which the heart, as a result of a functional or organic disorder, may so influence the circulation as to provoke congestion, passive or active, of the thyroid and produce what Révilliod has termed a "cardiac goiter."

This indicates that a careful study of the heart is necessary where, as is so often the case, a functional disorder, including the more prominent sign of hyperthyroidia, tachycardia, is present. Thus, a low vascular tension due to general vasodilation, may, in virtue of Marey's law, produce a rapid pulse and lead the clinician to believe that he is dealing with a goiter which has assumed the hyperthyroid or thyrotoxic type. On the whole, a rapid pulse does not always preclude treatment for simple goiter—with cardiac complications perhaps—unless the tachycardia be accompanied by other symptoms of larval Graves's disease.

When a cardiac disorder of an adynamic type, especially dilatation of the right ventricle, is detected, the iodides are safer than thyroid gland. Unless the rare type of "cardiac goiter" be present, digitalis is of material help in the curative process; digitalin, $\frac{1}{10}$ grain (0.06 Gm.) twice daily, not only enhances the cardiac dynamism, but tends also to regulate the *vis à tergo* motion of the blood in the body at large and thus relieve the congestion of the thyroid—a prominent feature of the enlargement of this organ which constitutes goiter.

In rebellious cases the injection of boiling water into the goiter may be tried. Porter's method previously described (see page 237) may be employed. John R. Wyeth[63] recommends the following method: The skin and the area to be injected are anesthetized by means of novocaine solution, one-half of 1 per cent. A steel syringe is filled with boiling water from a caldron, and the water immediately injected by inserting the needle well into the substance of the mass. To prevent scalding of the skin, the contiguous surfaces are shielded by a covering of towels, only the point of injection being left exposed. As the steam or water is apt to escape from the needle, a gauze swab is held as a shield in front of the needle, which is thrust through

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[63] Wyeth: New York Medical Record, May 29, 1915.

and into skin when the contact is made. From ten to twenty minims are forced out in one spot; after which the needle is partially withdrawn, the point carried to a new field, and the injection repeated. Three or four such areas may be injected at one sitting; injections are repeated as required, at intervals of one or two weeks, until the tumor disappears. In a case cited five injections were made in ten weeks, and in three months the goiter had entirely disappeared. Important vessels and nerves, as well as the trachea, should, of course, be avoided, and it is advisable not to point the needle immediately under the skin, as the excessive heat so directly applied may produce necrosis. A Bunsen burner or alcohol lamp held under the barrel of the syringe just as the needle is being inserted will insure the high temperature required. Care should be taken to avoid the veins.

Electricity sometimes proves of value, but only as an adjuvant to internal treatment. Galvanism may be administered by applying one of the electrodes, well moistened in saline solution, to each side of the goiter; 10 or more milliampères of the constant current should be used fifteen minutes every other day, the positive pole being placed over the goiter. For large growths, the electrodes should be broad and malleable, the one covering the entire surface of the goiter, while the other, well moistened, is applied to the back over the seventh cervical vertebra. A current of 20 milliampères or more is required to insure penetration. Cataphoresis may be carried out merely by wetting the negative electrode with Lugol's solution instead of saline solution. In most cases, however, especially where the general symptoms of hypothyroidia are not very marked, the internal administration of the iodide with galvanism will suffice. The latter contributes to the curative process by increasing the contractile activity of the blood-vessels, thus relieving the engorgement of the gland. Static electricity has also been used advantageously by some observers.

The X-rays have been tried, but the prevailing opinion is that they should not be used in hypothyroidia, their tendency being to inhibit further the functional activity of the gland—to the point of myxedema in some instances. Especially is this danger to be borne in mind in the case of goitrous children.

Vaccine therapy offers a promising therapeutic field in goiter. McCarrison,[64] in studying the amebic flora of the intestine in cases of endemic goiter in India, was led, by the uniformity of the bacterial growth, to try the effects of a vaccine made from this composite growth upon some of the cases. There followed a prompt decrease in the size of the enlarged gland and complete recovery in many cases. Upon examination of this bacterial growth it was found to consist mainly of a somewhat altered type of colon bacillus. He therefore used a vaccine made from this alone, and obtained similar good results. He also tried the effects of a vaccine made from a staphylococcus and one from a spore-bearing bacillus, with favorable results from both. He treated 33 cases in all, with most excellent results, but calls attention to the fact that the treatment is suitable for recent cases of parenchymatous goiter only, *i.e.*, the hypothyroid type. The results were best when the composite vaccine was used. By way of explanation of the action of these varied vaccines, he suggests that the cases studied by him in India, were due, as he had previously found, to an ameba in the intestine; that the thyroid is the means of combating certain toxins normally present in the intestine; that when to these there is added the specific virus of goiter (from the ameba) there is an extra strain put upon the gland, and in consequence of this it undergoes hypertrophy. By the use of one of the vaccines, which in itself is in no way specific for goiter, there is removed from the thyroid gland the added strain of neutralizing the toxins arising in the intestine from the bacteria there present, and the gland is able to return to its normal size and take care of the specific toxin of the disease. This interpretation is in accord with my own, the amebic toxin acting as pathogenic agent, which the vaccine combats by promoting the formation of antibodies, thus relieving the need of excessive thyroid activity.

Langmead[65] tried vaccines prepared from coliform bacilli from the patient's own bowel in eight cases of parenchymatous goiter. The growth disappeared in one instance and diminished in size in the rest. The initial dose was usually

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[64] McCarrison: London Lancet, Feb. 10, 1912.

[65] Langmead: Monthly Cyclopedia, May, 1914.

125 millions, increased by 25 or 30 millions at each injection administered weekly.

The diet is an important feature in some cases; meats should be partaken of sparingly owing to their tendency to raise the blood-pressure in some cases, and in others totally omitted if the case be one due to autointoxication of intestinal origin. Violent physical exercise produces the same effect as meats by increasing abnormally the average of wastes.

HYPERTHYROID OR TOXIC GOITER.

In the group of parenchymatous or simple goiters it is now customary to include—though injudiciously, since they thus tend to be overlooked, to the detriment of the patient—the considerable number of cases in which certain symptoms of thyrotoxicosis, in particular those relating to the heart, occur, nearly always, however, in the absence of exophthalmos. In my opinion, most if not all these cases are instances of larval exophthalmic goiter—this being sustained by the fact that the usual treatment for their condition is alone beneficial.

According to Brenizer, hyperthyroidia or thyroid toxemia is observed in 20 to 25 per cent. of all cases of simple goiter. The condition occurs most frequently in cases of diffuse or encapsulated adenoma of the thyroid of several years' standing. The toxic symptoms may arise either gradually or suddenly. The entire group of these cases has been termed by Plummer "toxic non-hyperplastic goiter," thus emphasizing the need of considering separately from simple goiter. Moreover, experienced clinicians are in accord that the state of the patient approximates more and more that of exophthalmic goiter, and the same preliminary measures and precautions as are necessary in the latter condition are indicated in *bona fide* cases.

Treatment.—When a goiter is showing a tendency to assume the Graves syndrome, Fowler's solution, 2 to 3 minims (0.12 to 0.18 c.c.), three times daily in half-glassful of water, or the bromides to reduce the sensitiveness of the centers, and cold compresses over the gland are useful. But if tachycardia, tremors, etc., persist, the treatment for Graves's disease (*q. v.*) should be employed. Thyroidectomy or at least ligation of some of the arteries of the thyroid should be performed if the less radical measures which usually succeed in Graves's disease fail.

L. F. Watson,[66] of Oklahoma City, obtained good results by injecting 10 to 40 c.c. (15 to 60 minims) of a sterilized 30 to 50 per cent. solution of quinine and urea hydrochloride into the growth, in fifty cases of hyperthyroidia. He recommended the method only to relieve the latter condition and not to remove the goiter, though the latter may disappear, when small. The injection must be used with discretion; its indiscriminate use by an inexperienced person might have bad results. The use of local anesthesia cannot be too much emphasized, and he precedes it in all toxic cases with preliminary injections, into the most prominent parts of the goiter, of a few minims of sterile salt solution, followed by sterile water injections. Two to four preliminary injections will accustom the patient so that the quinine and urea can be safely given with slight discomfort. As soon as no hyperthyroidal reaction follows the water injections their usefulness is over. After the usual aseptic precaution and the anesthetization of the site of the injection with a 0.1 per cent. cocaine, or a 0.25 novocaine solution, the needle is carried down to the body of the goiter, repeating the injections every third day, according to the progress of the patient. From 8 to 15 injections are usually necessary to bring about marked improvement. In cases of recent cystic goiter with moderate hyperthyroidism he aspirates the fluid and makes from 1 to 3 injections. In his conclusions he says the injection will not relieve advanced cases when the vascular and nervous systems have been permanently damaged, and, while the method is harmless in experienced hands, it should be used only in a hospital.

HYPOTHYROID DEGENERATIVE GOITER.

This type of goiter may occur as a morbid development of the simple or parenchymatous form reviewed above, but it does not, as is the case with the latter, represent a uniform pathological entity. The characteristic alteration may occur in one or several parts of the gland, thus giving it in most instances an irregular or nodular surface. The affected areas may be the seat either of an increase of follicles, vessels, etc., a true hypertrophy, or of accumulations of more or less thick and tenacious colloid, which dilates one or more follicles. These areas, especially when a single nodule is present, tend to degenerate owing to the influence of the proliferated tissues upon the neighboring structures and upon the local vascular supply, and to become the seat of hemorrhages. Nodule of the isthmus is relatively frequent, the mass projecting from the middle of the neck.

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[66] Watson: Jour. Am. Med. Assoc., Jan. 10, 1914, and Sept. 25, 1915.

As goitrous masses may develop anywhere in the gland, and simultaneously in several parts of the organ, while varying greatly in shape and size, the pressure effects they produce vary greatly with each case. The trachea may be displaced from side to side, twisted, or compressed against the spine, thus producing dyspnea; the cervical vessels and the vagus may also b pressed upon, causing congestive disorders of the brain, syncope slowing of the pulse and dyspnea. Hoarseness and aphonia ma occur, if the recurrent laryngeal is pressed upon. Occasionall sympathetic nerves are compressed, thus giving rise to vascula phenomena or paralysis in the parts which these nerves supply

The progress of recent years in the treatment of degenera tive goiter renders it necessary to identify its various forms some being amenable to measures which cannot be used in others Thus, while aspiration is sometimes possible in cystic goiter, i is of course unavailable in fibrous goiter, etc. The various type are as follows:—

Colloid Goiter.—This form of goiter, which is often me with in practice, is thus termed because its main characteristi is an accumulation of thick, tenacious colloid in follicles of th organ, in isolated lobules, lymph-spaces, and even the whol organ. In the average case the gelatinous colloid (the growt being termed *struma gelatinosum* by some authors) so overfil the follicles that the goiter is lobulated and hard. It is probabl an advanced stage of the softer goiters, both diffuse and nodula and may be distinguished from them through their relative har ness and the fact that they do not become reduced under pre sure with the hand, owing to escape of a part of the fluids i the neighboring tissues, as do some of the softer growths. Th form of goiter is not influenced by internal medication, iodin thyroid, etc.

Cystic Goiter.—This form may develop from a colloid goiter or from an *adenomatous goiter,* a form in which the glandular epithelium is embryonic and produces but little colloid. It may be composed of retention cysts or of *hemorrhagic cysts* due to rupture of some dilated vessels in the growth. This constitutes a special form of goiter.

Cystic goiter is lobular, sometimes oval, at others circular, but always circumscribed. It is elastic, and usually soft and smooth. Fluctuation may sometimes be elicited. Hence the fact that it may be aspirated and successfully treated without resorting to surgical removal.

Fibrous goiter differs entirely from the foregoing pathologically in that it is due to the development of fibrous tissue, a result of local inflammation in various parts of the organ. It is, therefore, hard under pressure and nodular. The glandular elements being more or less compressed by the fibrous tissue, their functional power is inhibited, causing a corresponding degree of hypothyroidia, which, when advanced, may reach the stage of true myxedema. In rare cases the goiter becomes as hard as wood; hence the terms ligneous goiter and Riedel's disease sometimes attributed to it. A distinctive feature of the latter is its rapid evolution—a few months or even weeks, serious pressure effects (described below) developing promptly.

Any one of the above types of goiter may, through projection of one or more parts of the gland, awaken a special group of phenomena most of which are serious.

Intrathoracic Goiter.—This type, which is by no means rare, is the result of a downward development of a nodule from either inferior horn of the thyroid. At first remaining above the suprasternal notch it finally passes down into the thorax, behind the sternum, being aided in doing so by the downward movement of the thyroid and the suction of the enlarged organ into the chest, which occur during inspiration. It is apt to be met in subjects who, owing to their occupation, are obliged to bend the head forward, as in writing, during prolonged periods each day, and in short-necked individuals.

As the intrathoracic goiter develops, tending as it does to become very large, the resistance of the sternum causes it to compress quite markedly the structures on either side of the tracelia and the latter itself, and may become a cause of sudden death.

The diagnosis of intrathoracic goiter is very difficult without the aid of X-rays. The most striking symptoms are dyspnea, dysphagia, hoarseness, cough, redness or suffusion of the face, cyanosis of the lips, dilatation of cervical veins and of those of the upper part of the chest. Cardiac symptoms, "palpitations," are usually complained of. Dullness over the manubrium sterni is also suggestive.

Constrictive Goiter.—In this form the nodular mass has grown in such a way as to pass behind the trachea and thus encircle or constrict it. It may also be due to embryonal malformation of the thyroid, both superior horns of which may encircle the trachea or esophagus. Dyspnea and dysphagia are the main symptoms. Deep laryngoscopy, esophagoscopy and the X-rays are of material help for the recognition of this condition —a very distressing one in most instances.

Lingual goiter is an interesting, though rare, form of goiter which is more frequent in women than in men, though in the latter accessory thyroids are more common. When these accessory structures become goitrous this occurs with relative suddenness, the growth showing great vascularity. Lingual thyroids are situated upon the dorsum of the tongue behind and below the foramen cecum and are sometimes very large. They cause prolonged fits of coughing, deglutition, spasms, and hoarseness.

Lingual goiter may be confused with malignant growths of the same structures. While lingual goiter is painless, however, malignant growths are painful and are usually accompanied by swelling of the neighboring lymphatic glands. They are apt moreover to grow more rapidly. The lingual gland at the base of the tongue may also be the seat of benign growths: dermoid cysts, calcareous deposits, etc., and gummata.

Hemorrhagic Goiter.—Although the thyroid gland is sometimes the seat of hemorrhagic foci in the course of certain infections, diphtheria in particular, the term "hemorrhagic goiter" is usually given to hemorrhage occurring more or less suddenly in a goiter. The minor vessels of these growths being delicate, a blow, a severe strain, violent coughing, playing wind instruments, glass-blowing, a fall, etc., cause them readily to tear. The resulting symptoms depend in intensity upon the size and location of the hemorrhagic focus, but as a rule they are severe, sufficiently so in some instances to end in almost immediate death. Swelling, tenderness, and pain due to distention, increasing dyspnea, cyanosis, asphyxia and other pressure symptoms follow in more or less rapid succession according to the location of the pressure and its degree and direction.

SYMPTOMS OF DEGENERATIVE GOITER.—Patients may be unaware of the existence of a goiter until some pressure symptoms among those described below, causes them to seek medical advice. Others complain of the necessity of increasing the size of their collarband; of disappearance of the normal circular creases of the neck; of stiffness about the front of the neck; of dyspnea on inclining the head forward, etc. The goiter being connected through the posterior capsule of the thyroid with the trachea and esophagus, deep respiration and deglutition cause the growth to move up and down, a fact which greatly facilitates its detection by inspection and palpation. Cough accentuates the movement and is especially helpful in the diagnosis of intrathoracic goiters. Detection of the latter is further facilitated by percussion over the upper part of the sternum, when marked dullness is obtained. If the goiter is sufficiently large to cause pressure on the trachea, a sibilant or whistling râle may be heard on auscultation. This is apt to be mistaken for asthma in cases of intrathoracic goiter occurring in short-necked individuals.

The diagnosis of a degenerative goiter is a relatively simple matter, even in their incipiency, when the measures described above are carried out. From the diffuse, simple, non-toxic growths, they are readily distinguished in most instances by the fact that they are nodular. While the former are, as a rule, diminished in size through pressure upon them, owing to the vascular depletion produced, nodular goiters yield but little, if at all, to pressure. Fluctuation may sometimes be discerned in large colloid or cystic growths.

Pressure symptoms are far more likely to occur in degenerative goiters than in simple goiters, because of their tendency, in addition to their general growth, to project nodules which directly or indirectly produce compression of some neighboring *structure, the trachea, esophagus, blood-vessels and nerves in particular. They may occur early or late in the history of the case, or suddenly where, as we have seen, interstitial hemorrhage is caused in the growth by a blow, violent effort, etc.*

Hoarseness is frequently observed in goiters that are sufficiently large to cause distortion of the trachea, compression upon the cricoid and thyroid cartilages, thus interfering with the proper anatomical relations. Hoarseness may also be caused by pressure upon the recurrent laryngeal nerve, and by a chronic catarrhal process of the laryngotracheal mucous membrane, due in turn to the pressure and the interference with the functions of the epithelium through which the membrane is kept free of foreign substances, mucus, etc.

Dyspnea, sometimes termed "goiter asthma," is a common and prominent symptom of goiters that have reached sufficient size to compress either the trachea, and thus interfere directly with respiration, or the blood-vessels of the neck and neighboring structures, thus disturbing the circulation and the equable return of blood to the heart and lung; or it may compress the recurrent laryngeal nerve. The dyspnea is increased by temporary hyperemia of the goiter or hemorrhage therein, by conditions which increase the demand of air, such as exertion, and by local catarrhal inflammation due to the pressure. When the trachea is markedly compressed, tracheal stridor, a loud, whistling sound may be heard during both inspiration and expiration. Paralysis of the vocal cords is frequent. J. Matthews[67] found in a laryngoscopic examination of 1000 cases, before and after removal of the goiter, 289 instances of partial paralysis and 272 of complete paralysis. Recovery of the vocal disability occurred only where the paralysis had been of short duration.

Asphyxia may readily be produced in such cases by sudden violent exertion, bending the head in such a way as to increase pressure of the growth on the trachea, sudden pressure on the growth, constriction of the neck, violent cough; hemorrhage into the goiter, thus suddenly increasing its dimensions; swallowing the wrong way, anger, by causing turgescence of the cervical vessels, etc. Cyanosis is not necessarily a symptom of threatening asphyxia, since it may also occur when the veins which drain the head, neck, and arms are compressed by the growth. The latter form may occur irrespective of dyspnea; it is apt to be especially marked during exertion. It affects chiefly the cheeks, lips, and tongue, and also the arms when the innominate veins are compressed.

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[67] Matthews: Jour. Am. Med. Assoc., Sept. 3, 1910.

Cardiac phenomena are frequent in goiter, as previously stated. The dyspnea is often increased by dilatation of the heart, due to the interference with the respiration. The heart should always be examined in these cases, since appropriate treatment is very helpful. Dilatation of the heart may also be due to pressure exerted by the goiter on the blood-vessels, and to the effects of defective nutrition incident upon the hypothyroidia upon its muscular elements.

Paralysis of various muscles of the arm, and numbness of the fingers, occasionally met with, are due to pressure upon the brachial plexus. These symptoms are mainly observed in intrathoracic goiter. Irritability, nervousness, restlessness, and other nervous phenomena may also be witnessed when hyperthyroidia is a feature of the case. Insanity is more frequent in goitrous than in normal individuals.

Myxedema may supervene when the functions of the thyroid have been sufficiently inhibited by fibrous and other degenerative changes, practically to arrest its functions. This complication is seldom witnessed until very late in the history of the case, unless the injudicious use of X-rays has totally inhibited its function, however, owing to the fact that a small portion of normal gland suffices to carry on its functions.

TREATMENT.—Under appropriate treatment, provided the causative intoxication be removed, good results are obtained in some cases of degenerative goiter—exclusive of course of the malignant types—especially when in young subjects, by the measures indicated for the simple form. The use of iodine requires, however, considerable care and should only be resorted to tentatively. In some types, the colloid for instance, any halogen or thyroid may give rise to untoward effects, owing to inability of the diseased gland to assimilate iodine. Cases of long standing, even though the goiter be small, are those most likely to react unfavorably to this form of treatment. All the other remedial agents described—injections of boiling water, electricity, galvanic or static; the X-rays, etc.—may be tried. In cystic goiters the aspiration of the contents of cysts can be resorted to and the reduction of growth thus greatly hastened. Removal of the causative intoxication, whatever that be, is essential, however, and sometimes affords surprising results. Especially is this the case when the source of intoxication is a focus of infection, such as chronic tonsillitis, or alimentary autointoxication, etc., which can be eliminated.

When the various measures indicated in simple goiter have been given fair trial and no result is obtained, surgical measures are indicated.

SURGICAL TREATMENT.*—The advisability of surgical treatment in goiter depends not only upon the type of goiter present, but upon the stage the disease has attained, the results which may be expected or have already been secured by medical treatment, the extent to which operation might reduce thyroid function below that required by the organism, and various other factors.

In simple goiter surgical treatment is occasionally demanded: (1) owing to the disfigurement, where the swelling is large; (2) because of symptoms due to pressure on the trachea, esophagus, larynx, or other structures in the neck or upper part of the thorax; (3) when enlargement of the goiter is rapid and a malignant nature is suspected; (4) when symptoms of hyperthyroidism appear; (5) when infection of the goiter occurs. Many patients come to the surgeon for cosmetic reasons alone. The risk attending operation in simple goiter being slight, radical treatment, *provided medical measures have proven ineffectual*, may be looked upon with favor in cases requesting it, —especially since a considerable proportion of simple goiters may subsequently undergo changes resulting in injury to the heart, kidneys, and liver, and possibly become cancerous in later life.

In the presence of mechanical symptoms, the patient is again often the best judge as to the time when the discomfort experienced is such as to require operation. Pain due to pressure, sometimes occasioned by hemorrhage within the gland, may be the chief symptoms indicating intervention. In the various types of non-exophthalmic, *i.e.*, non-toxic goiter, including colloid, parenchymatous, cystic, and general adenomatous conditions of the gland, definite indication for operation is afforded less by the size than by the location of the goiter tissue. At times a swelling not exceeding a cherry in size may cause urgent discomfort, whilst in other cases even a large goiter occasions no distress other than that of unsightliness.

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* This sub-section has been written by the author's son, Dr. Louis T. de M. Sajous.

Among the advantages of operation, where a definite indication for it exists, are its effect in preserving residual healthy thyroid tissue from destruction by pressure necrosis and the frequent resulting improvement in the heart action, even simple goiter being capable at times, we have seen, of inducing the well-known "goiter heart"—an effect usually attributed, though apparently often without justification, to pressure of the growth on blood-vessels in the neck.

Colloid and adenomatous goiters are, as a rule, but slightly responsive to medical treatment, and where pressure symptoms exist should be operated, the diseased part of the gland being removed and its better portions preserved.

In intrathoracic goiter with pressure symptoms, early intervention is indicated. Such a goiter, extending from either thyroid lobe, two or more inches beneath the sternum and into the thorax, particularly demands prompt operation, but is sometimes entirely overlooked or not detected until it is too late for operation.

The period of life at which a goiter appears has a distinct bearing on the operative indications. In particular, in the simple goiter met with in adolescents, a somewhat edematous type of colloid enlargement of the gland, operation is rarely indicated, as the goiter will often subside either with or without medical treatment. Severe dyspnea in goiter at puberty, however, is an indication for operation (Legg).

Most substantial goiters, however, cause cough, hoarseness, and suffocative attacks which lead eventually to their discovery through percussion and X-ray examination. Prominent veins extending from the neck down on the chest may also be noted.

Rapid enlargement of the thyroid in the form of an irregular, hard growth may occur, we have seen, because of hemorrhage, in a simple benign goiter, but is more generally indicative of carcinomatous or sarcomatous degeneration of the gland. Early operation is then required, as will be shown under the succeeding heading.

According to most surgeons, all goiters should be operated on when they are nodular, cystic, or beginning to adhere to neighboring structures, especially in adults. Removal of both lobes of the thyroid is, however, not required in innocent goiters. If both are enlarged, that which is the larger and extends lower and more deeply into the neck is the one to be removed. At times the lobe which is the cause of the symptoms, while extending lower in the neck, is the less enlarged of the two; this is, nevertheless, the one to be selected for removal. Where the trachea is displaced, that lobe which is the cause of the distortion should be removed.

In diffuse colloid and general adenomatous goiter, the removal of one lobe and of the isthmus is generally the procedure of choice, though in some instances removal of a portion of each lobe, as advised and practised by Mikulicz, is required. After the unilateral operation the remaining lobe generally undergoes later a reduction in size. Since, moreover, the extirpated lobe is that which is the most diseased, or exclusively diseased, the greater part of the enlargement can generally be removed without serious reduction of the properly functionating parenchyma.

In rapidly growing parenchymatous goiter in young individuals arterial ligation has been advised for the purpose of causing atrophy of the goiter tissue.

Encapsulated thyroid tumors may be removed by perforation of the gland substance and enucleation with the finger or a blunt instrument. This is generally the case in the largest substernal goiters. Encapsulated thyroid adenomata are apt to become cystic. Enucleation is, here again, the procedure of choice, tapping or injection, which might suggest themselves as simpler expedients, being inadvisable. Tapping may, however, be resorted to in the course of removal of a cystic substernal goiter, to facilitate its extraction from beneath the sternum. Even in freely movable goiters, provided they can be pushed down behind the sternum or clavicle, removal is considered advisable, as a prophylactic measure.

In large adenomata in which there is only a thin layer of thyroid tissue over an extensive area of the tumor the procedure known as "resection-enucleation" may be carried out, the portion of thyroid tissue over the tumor being left attached to and removed with it, and the cut edges of the gland then united with sutures.

Operative Risks and Results.—The mortality in operations in uncomplicated simple goiter is only a fraction of 1 per cent. The safest type of all cases for operation is that where the tumor is rounded and rather even in outline, *i.e.*, typically where it is cystic in nature. Firmness of the thyroid enlargement is a favorable feature, meaning that the gland has a strong capsule and that the removal can be effected easily.

Risk increases, on the other hand, where the trachea has been compressed for some time, with resulting bronchitis, emphysema, poor oxygenation, and impairment of cardiac action. The latter unfavorable condition may also be a result of marked interference with venous return through pressure on large vessels at the thoracic inlet, particularly if thrombosis has occurred, or of disorders such as atheroma of the coronary vessels or fatty heart. In all these cases cyanosis and puffiness of the face manifestly more pronounced than would reasonably be expected in view of the size and situation of the existing thyroid tumor are likely to be met with.

The danger of operation on the thyroid is also increased when the organ is in a condition of diffuse follicular colloid degeneration, the proportion of normal glandular tissue being greatly reduced. These are often large, nodulated goiters, pressing on the trachea and only slightly movable. Vascular ligation followed by unilateral excision is the best procedure in these cases to minimize danger.

According to Mayo, hemorrhage, either primary or delayed, with the efforts made to control it, constitutes the most important cause of death in operations for adenomatous goiters. Inclusion of some muscle tissue in ligation of the superior thyroid artery seems to have been usually responsible for delayed hemorrhage. Fortunately, patients with adenomatous goiters nearly always can withstand serious hemorrhages. The opposite is the case, on the other hand, in advanced and complicated cases of exophthalmic goiter. As for the danger from injury or removal of the parathyroids, *care to preserve the posterior capsule,* especially if in colloid goiter, both lateral lobes of the gland are operated on, is the chief prophylactic requirement.

Other possible causes of danger or death in thyroid surgery are acute thyroidism, collapse of the trachea due to absorption of cartilage through pressure, and such more general conditions as shock, air embolism, hemorrhage, pneumonia, infection, and anesthetic intoxication.

The author of the present work is not of the opinion, however, that the belief that "acute thyroidism" actually occurs when collapse follows thyroidectomy is well grounded. He ascribes the collapse to shock and has saved life, where "thyrotoxicosis" had been thought to exist by the surgeon, by at once resorting to hypodermoclysis and the simultaneous injection, into the rubber tube of the saline solution apparatus, of drop by drop of 20 minims of 1:1000 solution of adrenal chloride. Recovery is almost immediate under these conditions.

Acute inflammation of the thyroid, with or without adjoining structures, contraindicates thyroidectomy for the time being, incision and drainage being required as in other local infective conditions.

The useful results of radical treatment in simple or malignant goiters consist in the removal of a source of discomfort, physical deformity, dyspnea, hoarseness, and frequently of danger to the patient's life. In simple goiters with bilateral thyroid enlargement, removal of one lobe and the isthmus will generally be followed by shrinkage of the remaining lobe. In malignant tumors of the thyroid, a cure, if effected, will usually be obtained only where the condition is incipient and has not been suspected before operation.

MALIGNANT GOITER.

Malignant goiter is found, as shown by the records of the Mayo clinic in less than 1 per cent. of cases of goiter subjected to operation, and in 4 per cent. in Crile's cases (1917). In most instances, it appears in a simple goiter of long standing. Both carcinoma and sarcoma are witnessed, the latter being much rarer than the former. Diffuse malignant adenoma of the thyroid is a rare form which, owing to its lobulated surface, resembles simple colloid. It differs from the latter, however, in recurring after removal.

Malignancy is suggested by the occurrence of pain in a pre-existing goiter, when this symptom cannot be traced to strumitis, *i.e.*, inflammation of the goiter *per se*, especially if the cachectic facies is present.

The surrounding lymph glands are apt to be involved early. Metastases seem to show a predilection for the osseous system, but the morbid process tends gradually to involve neighboring organs, including the trachea and esophagus and to entail perforation of these structures. Suggestive of cancer, in addition to those due to pressure by a sufficiently enlarged or nodular gland, are radiating pain, hemoptysis or hemorrhage, traceable to congested pharyngeal vessels or tracheal or esophageal ulceration, or both, where there is a tracheo-esophageal fistula, and the regurgitation or expectoration of pus and detritus. Sarcoma may present itself as a smooth tumor, while a carcinomatous goiter is usually nodular.

TREATMENT.—Early operation is indicated in thyroid cancer, the whole gland being removed, but respecting the capsule whenever possible. In late malignant disease of the thyroid with lymphatic involvement, operation except for the relief of pressure symptoms is hardly to be recommended, as the development of the tumor may be hastened thereby. The immediate results are likely to be good, but recurrence is almost certain.

Goitrous accessory glands, especially those lying between the trachea and esophagus or behind the esophagus, may become the seat of malignant tumors and cause correspondingly grave pressure symptoms. Others lying between the hyoid bone and aortic arch, and which resemble lymph-glands, may also be the seat of goitrous development, occasionally malignant.

Enlarged accessory thyroid bodies can be identified only with difficulty if the enlargement corresponds, as to location, with one of the thyroid. As a rule, however, their abnormal location suggests the presence of accessory-gland goiters.

CONGENITAL GOITER, OR GOITER IN THE NEWBORN.

Contrary to the prevailing opinion, this form of goiter is not infrequent and is often fatal, owing to pressure on the trachea, nerves, and blood-vessels of the cervical area. According to Gonnet,[68] Demme, in 642 cases of goiter, found 37 in the newborn and 59 in infants from 2 to 12 months of life. Diethlin, in 2292 cases of goiter, observed the condition in 25 cases during the first year. Richard found 43 cases of really congenital goiters. Thévenot reported 130 cases.

In some infants the goiter is purely congestive, owing, probably, as occurs during parturition, to pressure upon the infant's neck, especially in face presentations and when forceps are used. It may also be due to persistence of the fetal circulation, but in most instances is of the parenchymatous type and is inherited. Gonnet, summarizing the cases reported by Demme, Richard and his own in this connection, states that out of 113 instances of congenital goiter 67 were in infants whose parents were goitrous. In 6 cases reported by Mooney[69] the mothers were all goitrous. This is readily accounted for by the fact that the same toxic influence which caused goiter in the parent also caused it in the offspring. In some infants the goiter encircles the trachea sufficiently to compress it and interfere with respiration, constituting a true constrictive goiter. It may also include the esophagus, in its grasp, insinuating itself behind it, even though appearing but slightly or not at all externally.

Symptoms.—In a goitrous infant death may occur almost immediately after a few efforts at respiration. Many are born prematurely, or are stillborn. Or, the infant shows signs of asthma, reaching in some instances to intense dyspnea with cyanosis, the child's cry being shrill or rasping. Death may occur suddenly immediately after the cord is ligated. When the goiter is due to simple congestion of the thyroid from compression or any other cause during parturition, or to screaming or writhing, it may disappear within twenty-four hours, never to recur in some cases; more frequently, however, it reappears intermittently. Dysphagia due to pressure upon the esophagus is not infrequent, the infant, in some instances, refusing to nurse.

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[68] Gonnet: Revue Mens. de Gynécol. d. Obst. et de Péd.; Surg. Gyn. and Obstet., Oct., 1909.

[69] Mooney: Archives of Pediatrics, Dec., 1910.

The clinical signs, with the exception, perhaps, of a slight swelling of the front of the neck, may not appear until several weeks or more after birth. The goiter may sometimes be felt, but in most instances it is quite small, and only discernible when the head is thrown back to stretch the neck, or during deglutition. In 130 cases in literature Fable and Thévenot found that the symptoms described were practically those observed in adults.

When the goiter is due to congestion from pressure, which may be suspected after face presentation or forceps cases, the prognosis is good, particularly if measures calculated to sustain oxygenation are resorted to. In true congenital goiter prompt surgical procedures will alone save life when the growth is of sufficient size to cause pressure symptoms.

TREATMENT.—The main indication is to restore respiration and sustain it. The various forms of artificial respiration with oxygen inhalations are very helpful. If, notwithstanding efforts in this direction, dyspnea recurs and persists, section of the isthmus, or exothyropexy, should be performed. The relief is immediate. The operation also leads to retrogression of the goiter.

Tracheotomy should never be resorted to, as it is often followed by bronchopneumonia, hemorrhage, or other complications. Intubation has been recommended by some authors.

In the congestive type cold compresses to the neck and warm foot-baths or hot baths tend greatly to reduce the swelling of the gland. In parenchymatous goiter which does not threaten life thyroid gland, 2 grains (0.13 Gm.) twice daily, administered to the nursing mother, causes gradual disappearance of the goiter in both mother and child in some instances. Sodium iodide, 5 grains (0.3 Gm.) three times daily, may be given instead if thyroid cannot be taken. A weak iodine ointment, rubbed gently into the goiter daily, avoiding cutaneous irritation, is also helpful. The tincture of iodine should not be used.

Pregnant women with goiter should be treated in the same way to arrest the possible development of a goiter in their offspring, and to prevent complications.

STRUMITIS, OR INFLAMMATION OF A GOITER.

Inflammation of a goiter may be caused by the invasion of bacteria and their toxins, brought to the goiter by the circulating blood in the course of various infections, particularly those which are seemingly benign: tonsillitis, laryngitis, bronchitis, and ulcerative nasal disorders, enteritis, etc.; though, as in acute thyroiditis, the more serious disorders—typhoid fever, diphtheria, lobar pneumonia, polyarthritis, puerperal sepsis, bacillary and amebic dysentery, Asiatic cholera, and other infections—may likewise provoke it, chiefly toward their close. Pathogenic bacteria seem to have an affinity for cysts and degenerated nodules. Traumatisms, punctures, even such as are practised when therapeutic agents are injected into a goiter, may also cause strumitis. It has also been ascribed to poisons, constituting the form known as "toxic strumitis."

SYMPTOMS.—Strumitis usually begins by a sensation of discomfort in the mass and a chill, soon followed by local pain, and marked sensitiveness to pressure. Then appear fever, headache, and the most distressing symptom of strumitis: dyspnea, sometimes threatening asphyxia. This is due to pressure of the swollen goiter upon the trachea, or to impaction of the mass between the sternum and the trachea, complicated often with edema of the larynx.

Dysphagia may also be marked and painful, each bolus in passing along the esophagus exerting pressure upon the inflamed gland. Radiating pains in the neighboring structures up to the occiput or down the arms, owing to pressure of the inflamed growth on nerves, is sometimes complained of. Hoarseness is frequent from the same cause, or as a result of glottic edema. If no pus be present, the inflammation tends promptly to subside.

When suppuration occurs the fever may assume the hectic type, with exacerbations and severe malaise and prostration. When this occurs in connection with a general infection, the prognosis of the latter may be markedly aggravated.

The inflamed goiter may become elastic and fluctuate if the abscess is large, which is often the case in strumitis. It may rupture into the surrounding tissues, open into the trachea, esophagus, the larger vessels, or, again, burrow down into the mediastinum, the lungs, pleura, etc., with its attendant dangers, or upward along the sheaths of the great cervical vessels. It may, however, open externally, to the great relief of the patient. Occasionally a small abscess is absorbed.

The only condition with which the strumitis may be confused is malignant growth, when softening, suppuration, and cachexia are prolonged. The course of cancer is not as rapid, however, and cultures and examination of fragments of the growth will usually establish the identity of the condition present.

PROGNOSIS.—The progress of the morbid process is governed by the intensity of the infection. Suppuration invariably prolongs the case, but if the abscess can be reached and evacuated the acute symptoms promptly subside.

A persistent abscess or a collection of them entail the dangerous phenomena enumerated above, which may cause death. Surgical measures, therefore, are indicated to save life.

TREATMENT.—The treatment is precisely the same as that recommended for acute thyroiditis, viz., cold compresses locally, and saline solution by the mouth or rectally to reduce the viscidity of the blood coursing through the organ. Chloral hydrate or veratrum viride used with care is advantageous to reduce the congestion of the organ, the former also acting as an analgesic by favoring sleep.

If symptoms indicating suppuration occur, the abscess if single, which is more frequently the case in strumitis than in acute thyroiditis, should be carefully located and evacuated. Kocher advocates excision of the goiter in such patients, if the surrounding tissues are not involved in the suppurative process. The operation should be preceded by an exploratory puncture and examination of the fluid, pus, etc., contained in the organ to ascertain that the bacteria therein, particularly the colon bacillus or the staphylococcus albus, are non-virulent. The pus should first be removed by aspiration and an antiseptic solution injected into the cavity. When the abscess has extended to the surrounding tissues, the sphacelous areas should be opened with the galvanocautery and the pus evacuated, but excision of the goiter would not be a safe procedure. The evacuation of the abscess should be done with due care, and the cavity washed out to remove all pus, rather than cleared with the curette or with the finger, which may provoke dangerous hemorrhage, as in a case observed by Bonney.

CHAPTER VI.

THE THYROID, THYMUS, PITUITARY, AND ADRENALS IN MENTAL DEFICIENCY.

IDIOCY AND MENTAL BACKWARDNESS IN CHILDREN.

IN treating this general subject, it will be necessary to refer briefly to a function of the adrenals which I first pointed out in 1903 and describe elsewhere in this work. I shall urge that the nerve-cell, *i.e.*, the neuron, should be regarded as an organ through which circulates, as elsewhere in the body, the albuminous constituent of the hemoglobin which I have identified as the adrenal secretion converted in the lungs into an oxidizing substance (adrenoxidase). This will be shown to react throughout the cell, with its phosphorus-laden myelin (supplied in turn with its nucleins by the thymus, as we shall see), the reaction leading to the production of nerve-energy. This energy, in turn, being the *sine qua non* of the functional activity of the neuron in so far as its efficiency as the organ of mind in the cortex is concerned, all conditions capable of interfering with the development of this energy through deficient activity of the ductless glands, or with the structure or functional efficiency of the neuron, will be introduced as so many factors capable of engendering mental deficiency.

The ductless glands being thus regarded prominent factors in the development of the brain and the maintenance of its psychic functions, it follows that toxemias, whether occurring *in utero* or after birth, especially those caused by certain infectious diseases of childhood, should, by provoking organic lesions, such as interstitial hemorrhage and its resulting fibrosis and atrophy, or by exhausting the organs, render them incapable of carrying on that nutritional function of the brain-cells and thus engender a corresponding degree of mental deficiency.

These two essential factors, added to those that have previously been established by the labors of others, seem to me to place the whole field of idiocy upon a more rational plane than *it has occupied heretofore. To make this clear, the pathogenesis of each form of idiocy treated will be considered in its relationship with the ductless glands. We shall see that this course will elucidate many mooted points and make it possible to identify clearly the stigmata of each gland involved in the morbid process as a causal agent, and therefore to point to the organic product or products indicated in each of the types of idiocy considered.*

THE THYROID APPARATUS IN MENTAL DEFICIENCY.

Cretinism, or infantile myxedema, was treated in full in the preceding chapter. This type of defective may be said to represent the characteristic form of thyroid idiocy, since, in *bona fide* cases that have not progressed too far, the disease yields to thyroid gland. Under the headings of Hypothyroidia and Myxedematous Infantilism we also reviewed larval and aberrant types of deficiency in which the thyroid apparatus plays the essential part. These disorders belong also to the class in which the thyroid gland is functionally deficient, the other ductless glands being also inadequate, but less so and only as a result of the primary thyroid deficiency, precisely as is the case in cretinism. There are types of idiocy, however, in which thyroid deficiency is either a concomitant or a result of deficient activity of other organs, and in which it is important to identify the stigmata which point to participation of both the thyroid and parathyroids in the morbid process. These thyroid stigmata will now be rehearsed in outline, however, to facilitate their recognition and the manner in which those other ductless glands merge with those illustrated.

Stigmata of Deficient Thyroid Activity.—As we have seen in the preceding chapter, hypothyroidia is the symptom-complex of thyroid deficiency. It seldom appears before the first year, especially in breast-fed infants, because they receive, through the maternal milk, enough thyroid secretion to compensate for any deficiency that their own gland may have acquired *in utero* or in the course of delivery. The earlier signs of hypothyroidia in infants are, in most instances, an unusual thickness of the neck, which may then lose its regular outline by swellings or pads due to localized myxedematous infiltrations. These pads may also be met in older children and adults. They frequently extend to the supraclavicular spaces and sometimes the axillæ. Obesity is suggestive when the skin is "pasty" or wax-like and dense,—a characteristic of myxedematous infiltration. The lips may be thickened and the lids and circumorbital tissues likewise, the eyes sometimes appearing unusually small. There is more or less delay, according to the severity of the case, in learning to speak and walk. The skin if thickened may become dry and scaly and the hair dry, coarse, and brittle, but only in cases in which the hyperthyroidia is marked. The nose may also remain squatty in such cases, and the child appear aged, *i.e.*, yellowish and wrinkled. The hearing and eyesight may be defective and the voice husky. The teeth are, as a rule, irregular and tend to decay early. The nails are short, thin, streaked, and brittle, and the hands broad and spade-like. The temperature is often subnormal and the extremities cold. The legs are unusually short and more or less bowed, while the general musculature is weak,—a fact which accounts for the constipation. Menstruation is frequently scant; in some cases, however, it is prolonged beyond the normal limits. In such cases metrorrhagia, epistaxis, and bleeding at the gums may also be witnessed.

Can all these symptoms be attributed to the thyroid only? While all of them may be observed in hypothyroidia, several bear the imprint of stigmata belonging to other ductless glands. Thus, as we shall see under their corresponding headings in the present chapter, the osseous deformities belong to the sphere of the thymus, while the muscular disorders, which include the intestinal, menstrual, and vascular atony, belong to that of the adrenals. As previously stated, however, they are secondary to the thyroid insufficiency, the secretion of this organ being a factor, as hormone, of the functional efficiency of the other glands, particularly in so far as their effects in tissues at large are concerned.

The stigmata of other ductless glands being isolated, we have left as belonging strictly to the domain of the thyroid:—

1. The subnormal temperature, cold extremities due to defective oxidation and metabolism, the thyroid collaborating actively with the adrenals and thymus (before puberty only as to the latter gland) in sustaining this process.

2. The myxedematous or doughy, dry skin, forming at times in cervical or axillary pads; due to plasmatic infiltration and circulatory torpor; also in very marked cases, the scaly skin and dry, brittle hair and nails, due to deficient nutrition of these structures.

3. The mental deficiency where true thyroid stigmata are discernible, complete development of the brain requiring perfect co-ordination of the thyroid, adrenal and thymic functions.

The importance of a clear identification of these specific signs will appear when the treatment of the various forms of idiocy other than cretinism, already reviewed, will be considered.

We shall now proceed to consider types of idiocy in which other ductless glands play the leading rôle. Prominent among these is the thymus. As this organ has not been considered so far, its physiological functions will first receive attention.

THE FUNCTIONS OF THE THYMUS.

While the thymus is a temporary organ in so far as its maximum activity is concerned, modern observations have demonstrated that its functions sometimes persist, though to a greatly diminished degree, to old age. It was at one time believed that its weight increased to the end of the second year, remaining thus until puberty. Hammar, of Upsala, showed, however, that if care were taken to study the organ in absolutely healthy subjects such as victims of accidents, suicides, etc., it would be found to increase in size from birth to puberty. At this time it averages in weight 25 grams. This represents a considerable increase, the average weight of the organ at birth being approximately one-fourth of this—5 grams (Testut), 6.7 grams (Thursfield), 13 grams (Friedleben). Bovaird and Nicoll,[1] in an examination of 495 consecutive cases, found, moreover, that while no decrease in weight occurred during the first five years, the organ could persist or continue to grow in the infantile state, the increase in size being thus a pathological condition. It is only, according to Hammar, when the thymus reaches 25 grams at puberty that it begins to diminish in size—rapidly from 15 to 25 years (5 grams), then slowly to 50 or 65 years, when it may weigh but 0.73 gram. In the aged it is represented by a small mass of adipose tissue in the anterior mediastinum—Waldeyer's retrosternal adipose body. It usually contains fibrous tissue and small patches or remnants of the thymic parenchyma, thus suggesting the possibility of continued function late in life. The discrepancies in the weights given by the various observers may be accounted for, to a certain extent, by the fact that what has been termed "accidental" involution of the organ may be produced rapidly at any time through starvation, illness, especially wasting diseases, exhaustion, etc. Such wide fluctuations, in fact, are not witnessed in any other organ, and have an important clinical bearing.

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[1] Bovaird and Nicoll: Archives of Pediatrics, Sept., 1906.

There is thus ground for the belief, sustained by considerable clinical evidence, that the functions of the thymus may not cease completely at puberty, and in fact persist, though perhaps to a very limited extent, to advanced age.

As to the function of the thymus gland, a general survey of the literature of the subject, experimental and clinical, evokes as leading clue some important relation with metabolism as regards the rôle of phosphorus in the process.

A suggestive feature in this connection is the influence of deficient thymic activity on the osseous system. Disorders of the thymus in which its functions are deficient or inhibited, growth, particularly that of the bones, is stunted. There are discrepancies in the reports of experimenters concerning the effects of removal of the organ; but if this is done completely and care be taken to avoid certain animals, rats for instance, in which supplementary ductless glands are frequently found, and the thymectomy is performed as soon as possible after birth, the results are sufficiently uniform to warrant their acceptance as sound factors in our inquiry. This has been emphasized by the recent labors of Basch (1906), Klose and Vogt (1910), Morel (1911), Matti (1912), and Lampé (1913). In dogs, bone deformities appear about the fourth month; the front paws curve inward and appear too short, while the back paws, also curved inward, appear too long. The cranium is large, flat, and short. Toward the fifth month the animal becomes somnolent, depressed, loses weight, and becomes cachectic, the morbid process progressing until, between twelve and eighteen months later, coma and death supervene.

The syndrome, in so far as the effects on the osseous system are concerned, recalls plainly that of rickets. The bones become soft and pliable, sufficiently so in some instances to cause them to yield, provoking various deformities, while the ligaments are elongated. The bones may be cut readily with scissors, in fact, until the cachectic period supervenes; flexibility then gives way to fragility and friability, the bones becoming very brittle. The bony tissue, we know, is deficient in lime salts. Osteomalacia is also characterized by softening of the bones in adults and occurs most frequently in nursing women.

These phenomena indicate clearly that thymectomy, rickets, osteomalacia, and other osseous disorders are all due to some impairment in the use of lime by the bones. Indeed, while we know that in the diseases mentioned there is a reduction of calcium in the osseous system at large, Bracci (1905) found that thymectomy caused a similar condition in the latter and in all tissues. Yet we are brought to realize that the morbid process must be due to *deficient use* of calcium by the structures, for Basch found that thymectomized animals excreted calcium in considerable excess. That this is all due to the absence of thymic influence was well shown by Sommer and Floecken in 1908, who found that the successful implantation of thymus in thymectomized animals caused resumption of skeletal growth.

Inadequate assimilation of calcium by the bones being self-evident, we are normally brought, knowing the cardinal rôle of calcium phosphate in the composition of bone, to look upon defective formation of this salt as the key to the morbid process. What is the nature of the relationship between the element linked to calcium, *i.e.*, phosphorus, and thymectomy? It is in this connection that light begins to appear.

A striking feature of thymic chemistry is the wealth of the parenchyma in nucleinates, its lymphoid cells, according to Chittenden,[2] containing a nucleoproteid rich in phosphorus, *i.e.*, 3.5 per cent. Hinskamp[3] also found that nucleohiston, which contains 3.7 per cent. of phosphorus, was the most abundant proteid in the thymus.

This wealth in phosphorus recalls another clinical phenomenon connected with the functions of the thymus, viz., the all-important influence which this organ seems to possess in the production of idiocy. At Bicêtre Hospital, according to Morel,[4] 75 per cent. of 408 non-myxedematous idiotic children, ranging from 1 to 5 years old, examined *post mortem* from 1890 to 1903, showed absence of the thymus. At the request of Bourneville, Katz[5] performed autopsies in 61 mentally normal children, in age from 1 month to 13 years, who had died of various diseases. In all of these the thymus was present conversely in 28 mentally weak children examined *post mortem* by Bourneville, the thymus was absent.

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[2] Chittenden: Boston Med. and Surg. Journal, Aug. 20, 1896.

[3] Hinskamp: Zeitschr. für physiol. Chemie, 1901.

These observations correspond with the results of complete thymectomy. Basch, Klose and Vogt, Morel and others observed mental disorders in puppies the fifth or sixth month after removal of the organ. The animals appeared idiotic and crushed, slow in hearing the voice or in understanding threatening gestures, or in recognizing their sleeping place or even their food. They showed great voracity, ate anything—cork, wood, cotton, etc.—and even gnawed their own tissues, their paws, penis, etc. All discerning power denoting intelligence seemed in abeyance. Concomitantly, both in idiotic children and lower animals, owing to absence of thymus, bony deformities such as those previously mentioned were frequently observed. That phosphorus in a fundamental constituent of brain-cells, as well as of osseous tissue, need hardly be emphasized.

We are thus dealing with an organ which, while itself capable of supplying nucleins rich in phosphorus, is clearly connected pathogenically when its functions are inhibited with disorders due to lack of phosphorus, such as rickets, retarded growth, idiocy, etc. The conclusion that the nucleins represent the connecting link between the gland and the tissues is self-evident.

Infantile marasmus has also been attributed to impaired activity of the thymus. In 18 cases of this disorder reported by Ruhräh[6] this organ was the only one which showed lesions. R. L. Thompson[7] also found marked thymic atrophy in 20 cases of marasmus in infants under 1 year old. Atrophy of the thymus is regarded by Dudgeon[8] as the most characteristic feature of the disease, a view concurred in by Rohrer, Bovaird, Nicoll, Warthin, Rachford, and others. Friedleben urged, as far back as 1858, in fact that "the size and condition of the thymus is an index to the state of nutrition of the body." From my viewpoint, however, this is a result of the marasmic state rather than a cause; since we know that starvation causes atrophy or contraction rather than enlargement of the gland. The rapidity with which some cases of marasmus recover when given proper diet, the breast, etc., also shows that the functions of the organ cannot have occurred by organic degeneration.

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[4] Morel: Paris médical, Jan. 17, 1914.
[5] Katz: Le Progrès médical, June 23, 1900.
[6] Ruhräh: British Medical Journal, Aug. 29, 1893.
[7] Thompson: American Jour. of the Med. Sciences, Oct., 1907.

As to the manner in which the thymic nucleins are furnished to the tissues, the older view that the thymus supplies the body a true internal secretion is no longer believed, all the methods used in the study of other glands such as the thyroid, the adrenals, etc., having failed to sustain it. The slight effect on the blood-pressure noted does not militate against this view; nor do even the beneficial effects obtained in various disorders due to deficiency or absence of thymic activity, from the expressed juice, extracts, or other preparations of the organ, since they all contain the characteristic nucleins. The bulk of evidence available points to another mode of transmission viz., *through the agency of lymphocytes which develop in the thymus.* What evidence have we to this effect?

The thymus is composed, as is well known, of lobules varying in size from that of millet seed to that of a small pea. Each lobule in turn is subdivided into small follicles (varying from 1 to 2 mm.) which constitute the functional structure of the gland. An important feature in the present connection is that each follicle is composed of two portions, the medullary and cortical. In the former, mainly composed of coarse reticulum, the cells, including the Hassall corpuscles, are relatively few. The important portion of the follicle in the present connection is its external or cortical portion.

The bulk of evidence at the present time (1916) favors the view of Stöhr, Weidenreich[9] and others, that the cortical portion of the thymic follicle is of epithelial origin and the source of lymphocytes, *i.e.*, small leucocytes containing a round nucleus which fills them almost completely. The earliest evidence that these cells are formed in the organ appears in the course of the third fetal month, when there appear numerous readily stained nuclei in the small thymic cells. The histological studies of Flemming, Prenant, and others have shown that these small cells multiply by karyokinesis in the most peripheral part of the cortical portion and ultimately become lymphocytes. In certain lower forms—Teleostei, for instance—the process of development of these cells may readily be traced, as shown by Maximow in 1912 and Fulci in 1913.[10] The thymus contains other cellular elements, but, as recently emphasized by Dustin,[11] these structures, the myoid, epithelioid, and granular cells, and also the Hassall corpuscles, are non-typical, inconstant, and auxiliary as to function. The only cellular elements which are constantly present in the thymus are the characteristic small "thymic cells" which become the lymphocytes.

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[8] Dudgeon: Jour. of Path. and Bact., vol. x, p. 173, 1905.

[9] Weidenreich: Münchener med. Wochenschrift, Nov. 26, 1912.

Modern researches are believed, by most writers, to show that the older view of Kölliker based on histological studies, and more recently revamped by Beard, to the effect that the thymus was the original source of lymphocytes and leucocytes which, according to these investigators, arose from the thymic epithelial cells, was erroneous. In the light of my own views the only flaw in the teaching of Kölliker and Beard is that they attributed to the thymus the power of generating *all* leucocytes.

The evidence submitted and much that could be added warrant only the conclusion that the thymus contributes lymphocytes to the general asset. This is shown by the fact that, in conditions in which lymphocytosis of thymic origin is met by thymectomy, all lymphocytes do not disappear from the blood, the proportion of these cells falling to normal. Or the percentage may decline to a certain figure; in a case reported by Schumacher and Roth,[12] for example, the lymphocytosis of a case of Graves's disease went down gradually after the operation from 46 to 34 per cent., but remained there. In another case, one of the thymic hypertrophy mentioned by Klose, Lampé and Liesegang,[13] the decline was from 68 to 73 per cent, after removal of the organ. The two latter investigators found, moreover, that diminution of the number of lymphocytes occurred after thymectomy in normal animals, thus showing clearly that the thymus contributed its typical cells to the circulation.

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[10] Fulci: Deutsche med. Wochenschrift, Sept. 11, 1912.

[11] Dustin: Annales et bulletins de la Société Royale des Sciences médicales et naturelles de Bruxelles, vol. lxxii, No. 5, 1914.

[12] Schumacher and Roth: Mitteilungen aus de Grenzgebeiten der Med. und Chir., xxv, 4, 746, 1912.

My belief that *the thymic lymphocytes are specific as to function* is based on many facts. Modern investigations are showing increasingly that the former belief that the human thymus was a lymphoid organ, *i.e.*, one similar in structure to the lymph-glands, was unwarranted, and that it is an epithelial organ. We are thus brought to realize that the thymic lymphocytes, which might thus be termed "thymocytes," are produced, in a special manner, *i.e.*, as previously stated, by epithelial cells. Chemically, as shown by Herlitzka and Borrino,[14] the thymic nucleohistons differ from similar bodies of other organs; they possess no glycolytic power and are unable to destroy glycogen. Bang,[15] moreover, found that the small thymic cells which develop into the so-called lymphocytes have a different reaction from those derived from other structures, the spleen, bone-marrow, and bones. "That the thymus-cells are not identical with those of the lymph-glands," writes Biedl,[16] "is proved by the fact that the amount of the nucleinates, the substances which are characteristic of the nuclear structure of the true glands, is *at least five times as large* in the thymus- as in the lymph- glands."

Apart from that of producing lymph-corpuscles which in the blood become lymphocytes—those which the thymocytes supplement during development—the functions of the thymus, as illustrated by experimental thymectomy, bear no resemblance to those attributed to lymph-glands. The influence of the thymus, as illustrated by this operation in animals, on the development of the osseous system, the mind, etc., previously described, has no counterpart in the functions of the lymph-glands. The latter, acting as filters of the lymph which passes through them, to rid it of bacteria, cell detritus, tumor-cells, etc., serve to destroy these harmful substances—though often destroyed themselves in the course of their protective rôle, as in syphilitic bubo, bubonic plague, tuberculous adenitis, etc. All these processes have nothing in common with those witnessed in the thymus. The clinic confirms physiological teachings that bone deformities, rickets, idiocy, and other disorders due to thymic inadequacy are in no way connected pathogenically with, or resembling, disorders of the lymphatic glands.

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[13] Klose, Lampé and Liesegang: Beiträge zu klin. Chir., lxxvii, No. 3, 1913.
[14] Herlitzka and Borrino: Archives Italiennes de Biologie, June 10, 1903.
[15] Bang: Hofmeister's Beiträge zu chem. Physiol. und Pathol., 4 and 5, 1904.
[16] Biedl: Internal Secretory Organs, p. 112, 1913.

Suggesting also that the thymic lymphocytes carry on an autonomous or specific function is the adaptation of its *main* activity to a temporary period, *i.e.*, that during which the body is developed, when it requires an excess of nucleins. Hence the extraordinary wealth of the thymus in nucleinates. As is well known, the phosphorus-laden nuclear materials are essential in the composition of the nucleus of every cell, the dynamic initiator as it were—with the oxygen carried also by a blood-cell to all tissues—of all processes considered particularly vital. Indeed, we are dealing here with a fundamental process concerning not only vital phenomena, but also, in my opinion, heredity. As emphasized by Kossel[17] it is the nuclein, the chromogenic portion of the nucleus, which initiates cell division and, according to present knowledge, hereditary characteristics.

Additional evidence of the constructive power of the thymic cells in their influence on bone growth is afforded by the fact that while thymectomy soon after birth is followed by defective growth and deformities, thymus, administered early, restores normal development. Indeed Gudernatsch[18] found that this substance fed to tadpoles prolonged their early growth markedly; the animals becoming unduly large, though metamorphosis, evolution of limbs, etc., was delayed. R. Webb Wilcox[19] obtained a gain in height of 9¼ inches in an undersized boy, also by the use of thymus-gland. The delay in the development of the brain, illustrated by the idiocy of thymectomized animals and of children with small or no thymus-gland, indicates its constructive influence in this organ. The genital organs are influenced in the same way. Thymectomy causes loss of sexual instinct and sterility and defective development of organs of reproduction;

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[17] Kossel: Münchener med. Wochenschrift, B. lviii, 65, 1911.
[18] Gudernatsch: Zentralbl. für Physiologie, xxvi, p. 223, 1912.
[19] Wilcox: Boston Medical and Surg. Journ., Aug. 13, 1908.

but the use of thymus counteracts this effect. Kerley and Beebe,[20] in a case of retarded development, obtained enlargement of the sexual organs, with growth of hair on the pubis and axillæ. In rabbits and guinea-pigs, as shown by Soederlund and Backmann[21] the thymus attains its greatest weight, while spermatogenesis is being prepared, and it is only when the sexual organs are developed that atrophy of the gland begins. The bearing of this asserts itself when we recall that, as illustrated by Kossel's labors, one of the chief sources of material for the study of nucleins has been the *heads* of spermatozoa of various animals. Spermatogenesis continuing, under normal conditions, throughout life, we are brought to realize that, as is the case with the bones, the brain and nervous system, the genital system and, in fact, the body at large, the thymic lymphocytes are specific in the sense that they are *abnormally rich in nucleus-building materials.* Their rôle is to add to the body during its evolution to puberty, or later if need be, the excess of nucleins required for this purpose.

Summarized these facts tend to substantiate the following definition of the function of the thymus, similar in its general lines to one first submitted by myself in 1903, in the first edition of the present work (page 182), before most of the confirmatory data adduced herein had been recorded:—

The function of the thymus is to supply, through the agency of its lymphocytes, the excess of phosphorus in organic combination which the body, particularly the osseous, nervous, and genital systems, requires during its development and growth, i.e., *during infancy, childhood, and adolescence or later if need be.*

We must not lose sight of the fact that besides being supported by the bulk of available evidence from various branches of biological science, this interpretation of the function of the thymus accounts for the many different rôles that have been ascribed to this organ, and which have led Howell[22] to state that "practically nothing is known concerning these functions."

STIGMATA OF DEFICIENT ACTIVITY OF THE THYMUS.—The foregoing data indicate plainly, from both the experimental and clinical aspects of the question, the specific symptoms or stigmata which indicate hypothymia. They are as follows:—

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[20] Kerley and Beebe: Amer. Jour. Med. Sciences, Aug., 1912.

[21] Soederlund and Backmann: Archiv für mikroskopische Anatomie, 73, 1909.

[22] Howell: Textbook of Physiology, 5th ed., p. 855, 1913.

1. Deficient development of the osseous system and deformities suggesting rickets or osteomalacia, due to deficient assimilation of calcium owing to the deficiency of thymic nucleins which take part in the building up of calcium phosphate. Deficient stature.

2. Deficient mental development entailing various grades of idiocy due to the insufficient production of thymic nucleins to supply the neurons of the central nervous system, during its development.

3. A low relative lymphocyte count owing to the inadequate formation of thymocytes.

In cretinism, as we have seen, most of the stigmata could be traced to the thyroid. This applies as well, I have found, to the stigmata of deficiency of the thymus, another form of idiocy that is now to be considered.

MONGOLIAN IDIOCY.

Mongolian idiocy, as its name denotes, is characterized by a striking resemblance of the little patient, even at birth, to a Mongolian, particularly the Chinese. The slanting eyes and the epicanthal folds are particularly noticeable. The distinguishing features of these cases coincide suggestively with physiological, pathological, and clinical phenomena traced to the thymus under the foregoing heading. The stigmata of deficient bone growth, so distinct in thymectomized animals, are very marked. Defective bone development is shown by the low average stature, the adult patient seldom exceeding 4 feet in height, due mainly to the fact that the long bones, particularly of the legs, are abnormally short.

Hence also the flat chest; the squatty nasal bridge; the small, undeveloped ears; the stubby, square hand, with its short, tapering fingers, the little finger being usually incurved. The skull likewise shows participation in the morbid process, the anteroposterior diameter being almost equal to the transverse, a fact which causes the head to appear round. It is, in fact, abnormally small. Although the forehead usually bulges anteriorly, the plane of the face and that of the occiput tend to parallelism. The circumferential measurements are invariably below normal, sometimes as much as two and one-half inches, the average being, in 26 cases studied by J. Muir,[23] one and one-third inches. This is an important practical feature, for the deficient skull development and the resulting reduction of brain capacity when the fontanelles are closed (which fortunately occurs late), tends to reduce the efficiency of therapeutic measures calculated to improve the mental status of the child.

Additional evidence as to defective bone nutrition is shown by the frequency of rickets, of which clear evidences are commonly discernible at birth. This applies also to other congenital defects such as club-foot, dislocation of the hips, etc. Palatal deformities are present in approximately two-thirds of the cases. The teeth, surrounded by hypertrophied gums, are irregular and undergo caries early, particularly in the low grades of the disease; they appear later, the second dentition being also delayed.

While these phenomena point clearly to the thymus as deficient, a similar condition of other ductless glands is suggested by stigmata which are deemed characteristic of deficient secretory activity of these organs. The thyroid seems to be one of these. Thus, while the skin may be dark and soft in some patients, in others it is dry and rough, as it is in cretins, even though allowance be made in these cases for the frequency of eczema—another proof of deficient catabolism. As in cretinism also, the tongue is thick and heavy, and protrudes more or less, but it is the seat of phenomena which some regard specific to Mongolian idiocy, though this has not been confirmed by my experience: transverse fissures and roughness; owing to greatly hypertrophied papillæ. The lips are usually thin, but they may also be thick and everted, though the body may not show evidences of myxedema. The tonsils and the nasopharyngeal glandular tissues are often found enlarged. Middle-ear disease is therefore common.

Subnormal temperature, with marked sensitiveness to cold and sluggish circulation, is another symptom commonly noted in cretinism, which also prevails in Mongolian idiocy, but the adrenals might likewise underlie these phenomena, owing to the marked influence on cardiovascular dynamism and on tissue oxidation. Indeed, the development of the entire musculature is considerably delayed, muscular power likewise. The ligaments are so loosely strung, in fact, as to permit the freest movements and contortions; the fingers, for example, may be bent backward upon the dorsum of the hand with the utmost ease. And yet all muscular movements are clumsy, being poorly co-ordinated, a feature which, in affecting the lingual musculature, contributes considerably to the retardation of speech. The ocular muscles are likewise involved, as shown by the frequency of strabismus and nystagmus in these patients. This applies also to the abdominal muscles, hernia, especially the umbilical form, being common. The abdomen itself is usually large and distended owing to relaxation of its musculature. Most striking is the frequency of cardiac atony, owing doubtless to the deficient supply of adrenal secretion.

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[23] Muir: Archives of Pediatrics, March, 1903.

We have seen that the nucleins supplied by the thymus and the secretions of the thyroid and adrenals took an active part in tissue metabolism and immunity. Since inadequate activity of these organs lowers the development and functional activity of the osseous, muscular and nervous systems, it should, therefore, also lower, in the light of my views, the defensive efficiency of the organism. That such is the case is shown in various ways. The Mongolian idiot is peculiarly subject to bacterial infections of the tissues most exposed to them,—the respiratory and intestinal tracts, the eyes, skin, etc. He is an easy prey, therefore, to tuberculosis, bronchopneumonia, pneumonia, influenza, and bacterial diseases of the intestinal canal, succumbing promptly under their effects. The twenty-fifth year is reached in but 9.4 per cent. according to Wiggandt.

Deficient metabolism initiated during uterine life accounts also for the idiocy. Along with the rest of the body, the intelligence lags behind, owing to deficient development of the organ of mind. The Mongolian infant is unusually well behaved, so good in fact as to elicit comment and favorable comparison with the average lusty baby. Small at birth, it develops about one-half as rapidly as the normal child, but its emotions are still slower in developing, in keeping with its powers of observation, which in some cases are virtually *nil* during the first year. It will lie in bed placidly hours at a time, apparently quite contented. As some evidence of mental activity appears, it follows a common trend. The child is not morose or torpid, as is the case with cretins; it is amiable and even affectionate, and often shows a remarkable predilection for music, dancing, and mimicry, though sometimes mischievously so. The imitativeness is sometimes so marked as to suggest atavism to a Simian type, a perpetual grin and frontal creases in some cases lending additional color to such a possibility. Important in this connection, particularly with a view to prophylactic treatment, is that the Mongolian cast of features is often noticeable very soon after, if not at, birth.

ETIOLOGY AND PATHOGENESIS.—The etiology of Mongolian idiocy is clear in only one direction, viz., that no special hereditary vice or disease is communicated to the child, though here and there syphilis, gout, violent emotion, and other disorders usually incriminated may be found in the near or remote parentage. Analyzing this point closely, however, we are soon brought to realize that such disorders are not direct factors in the genesis of Mongolian idiocy, though ancestral neuroses or parental emotions may add some influence to that which seems seriously to impose itself—parental unbalance or procreative asthenia. Thus, the majority of these cases occur as offsprings of couples that have been prolific, the little Mongolian being the last brother or sister of many normal children. Leeper,[24] for example, in a study of 176 Mongolian idiots found that one-half of them were the last-born of large families, and that neuroses were common in their ancestral histories. Again, they will occur as the product of aged couples or where there is a marked disparity in ages. To use a homely comparison, the factory is worn out *in toto* or in part, and the product is below par. This is illustrated by the characteristic facies of the Mongolian child, which is that of all other patients of the same special class. They look alike to such a degree, in all countries, that they might be taken for closely related members of a single family.

Suggestive from the standpoint of etiology in its bearing upon the pathogenesis and treatment of Mongolism is the fact that the Mongolian facies may not be due to mere hazard. A deeper search into its causes than has been accorded this phenomenon so far has led me to a pathological factor of a biochemical order quite in keeping with observed facts. Indeed, if our knowledge of the dietetics of the Mongolian branch of the human family is taken into account, many of the morbid phenomena so common among the poor of that race seem plainly ascribable to what hygienists have termed an "unbalanced diet." As is well known, lack of fresh fruits and vegetables, with a preponderance of salt meats, causes scurvy, and beriberi results from a monotonous diet, of which unpolished or unmilled rice is the main component. But we are aware also that rickets and marasmus are produced through lack of animal and an excess of starchy foods. Now, the Mongolian race, and particularly that part of it composing the "coolie" element in Asia, shows indubitably the subtle influence of centuries of unbalanced diet. The polished rice which constitutes their main diet fails to furnish them, owing to the absence of the pericarp sacrificed in the milling process, an adequate proportion of elements necessary to the physiologically perfect organism.

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[24] Leeper: Review of Neurology and Psychol., Jan., 1912.

Prominent among these is phosphorus. The labors of Fraser and Stanton,[25] Aron,[26] Dehaan,[27] and others have shown that the outer layer of the rice, the pericarp, removed during the process of milling, is precisely that which contains soluble organic compounds rich in phosphorus. Conversely Bréaudat and Denier[28] found that the administration of this pericarp in the form of rice bran proved prophylactic against the development of beriberi; it has also been used as a cure for the disease by Heiser[29] and others. Briefly the deficiency of phosphorus in the form of phosphorus pentoxide in milled rice has been identified as the passive cause of beriberi. In individuals who, through a long line of forbears, have become habituated to its use, with perhaps a little fish, as main diet, as is the case with the bulk of rice-fed Asiatics, phenomena of another order become manifest, viz., those of deficient development of tissues in which phosphorus is the preponderating agent, the *osseous and cerebrospinal systems and also primarily of the thymus gland, which, through its nucleins, insures the development of these systems.*

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[25] Fraser and Stanton: Lancet, Feb. 13, 1909.

[26] Aron: Philippine Jour. of Science, vol. v, p. 81, 1910.

[27] Dehaan: *Ibid.*, vol. v, p. 65, 1910.

[28] Bréaudat and Denier: Annales de l'Institut Pasteur, No. 2, Feb., 1911.

[29] Heiser: Jour. of the Am. Med. Assoc., vol. li, p. 1237, 1911.

Analyzing the pathogenesis of Mongolian idiocy from this standpoint, the kinship between the characteristic features of this disease and the attributes peculiar to rice-fed Mongolians is striking. The small size of the Japanese, Siamese, Tonkinese, Annamites, etc.; the slanting eyes, the narrow palpebral fissure and the epicanthus, especially marked in the Chinese, and the high cheek-bones are all peculiar to the Mongolian idiot. In the "yellow race," so called, the skin is pasty, yellowish, doughy, but smooth; the hair is straight; the nose is squatty, exposing the openings of the nostrils—all morphological characteristics of the Mongolian idiot. Another peculiarity of the latter is his predilection to infection and the deficient resistance shown to infectious diseases; we know how readily rice-fed Asiatic coolies acquire such diseases and succumb to them.

That the mentality is not necessarily dwarfed in the rice-fed Asiatic, as it is in the class of patients in question, is doubtless due to the adjustment of his nervous system to his deficient diet throughout the thousands of years he has employed it. But there is greater disparity between the lower and the higher classes of Asiatics in this particular than there is among the white races, owing doubtless to the greater variety of foods the upper classes utilize in Asia, which causes them to avoid unconsciously the harmful influences of a deficient intake of phosphorus. This probably accounts also for the fact that these upper classes seem, in most instances, not to resemble their ill-fed compatriots, the slanting eyes, squatty nose, etc., being less frequent among them.

PATHOLOGY.—In typical cases the brain and, in fact, the entire nervous system show no organic lesion other than imperfect cellular and general development, varying in degree with that of the mind. The osseous system is also the seat of nutritional lesions varying in degree with the severity of the case. Shuttleworth[30] has aptly referred to these characteristic examples of the disease as "unfinished children." The condition of the thymus has not been studied at autopsy in a sufficient number of clearly defined typical cases to warrant definite conclusions, but percussion and radiography suggest absence or atrophy in some and hypertrophy in other cases. The latter form probably represents an effort at compensation, what remains of the thymus undergoing compensative hyperplasia—precisely as does the thyroid in hypothyroid goiter. This is further suggested by the fact that puberty may be precocious in these cases.

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[30] Shuttleworth: Quoted by McKee and Wells: "Practical Pediatrics," p. 622, 1914.

TREATMENT.—Mongolian idiocy is generally considered about the most rebellious form of idiocy, judging from the literature of the subject. Comby,[31] for example, who urges rightly that it is more frequent than is believed, writes that the results of treatment have not been found encouraging. Some good, it is stated, may be effected by hygienic means, especially good and substantial nourishment and country air, while in mild cases satisfactory results may be obtained by appropriate education. Other authors have tried in turn: thymus, thyroid, the iodides, mercury, etc.,—the whole gamut, in fact, of agents suggested by any possible etiological factor that the history of a given case might indicate,—but without avail.

Our efforts should tend, if better results are to be attained, in two directions: prophylactic and remedial.

As to prophylaxis, we should be constantly on the watch for Mongolism when the causative conditions—aged parents, marked discrepancy in the age of parents, prolific parents with the new infant as last offspring, strong mental emotion or affliction in the mother, syphilis and alcoholism—are features of the parental history. A very quiet and "good" baby, giving the parents so little trouble that they take pride in mentioning it, may be found on examination to show the facial characteristics of Mongolism. This diagnosis may then be further suggested by the presence of unusually loose joints, as shown by an abnormally wide range of motion, unusual helplessness and muscular asthenia, indicated by inability to hold up its head. Treatment of the infant through the nursing mother is then indicated. As will be shown in the second volume, organic products are transmitted to the child through the maternal milk. This may be taken advantage of to modify the trend of the infant by supplying to its body those it needs for its development. Thymus gland 5 grains, thyroid gland 1 grain, and pituitary gland 1 grain, to replace adrenal gland advantageously, three times a day *during* meals, with a varied diet, and, as much as possible, out-of-door life may be given. Where maternal nursing or wet nursing cannot, for good reasons, be carried out, *direct nursing, using goats' milk* in some such way as that carried out in Italy, Egypt, South America, and other countries. If an intermediate electric milking apparatus is used, *cows' milk, which is well tolerated by infants when fresh from the udder,* can be used, the milk being pumped into the nursing bottle in quantities required, adjusted to the age of the infant. Organic preparations finely powdered, if dry, may be consequently dissolved in milk thus given.[32]

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[31] Comby: Archives des Maladies des Enfants, April, 1906.

The older the patient when first seen, the smaller the chances of success. Yet in all *some* improvement is obtained, particularly as to growth and any cutaneous disorder that may be present. The doses mentioned for a nursing mother are suitable for a child of 5 years, but the dose of thymus may be increased gradually until, if need be, 15 grains (1 Gm.) are given three times daily. If the stigmata of either one of the three ductless glands involved in the morbid process appear more prominently than those of the other two, the dose of the organic preparation representing that gland should be increased.

Removal of enlarged tonsils and adenoids is always indicated. It enhances progress even as regards the mental condition in some instances. Syrup of the hypophosphites to promote the nutrition of the cerebrospinal system and iron to assist in building up the hemoglobin are of signal advantage. A substantial and varied diet is likewise indicated.

The mental status may be materially improved, but at the cost of much patience and perseverance, though the Mongolian idiot is usually a good worker. The imitative instinct of the little patient should be taken as starting point of a systematic education, selecting a special line of work, music for instance, to which the child is normally attracted, as main aim. He should not be deprived of the company of normal children, the excitement and fun involved and the out-of-door exercise doing much to enhance the functional activity of his ductless glands.

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[32] Sajous: New York Medical Journal, page 1128, May 29, 1915.

THE ADRENALS IN IDIOCY.

One of the most striking features of *anencephaly,* a monstrosity (shown in the annexed illustration) characterized by absence of the brain and spinal cord, is the fact that the adrenal cortex is so poorly if at all developed that the absence of this portion of the adrenals may be predicated with practical certainty. It may also be diminutive or absent in certain forms of idiocy. Thus, as Apert[33] states, "atrophy of the adrenal cortex is the rule in anencephaly. Since this was first observed by Morgagni it has been verified in hundreds of cases of anencephaly, pseudoencephaly, cyclopia, and even in a few instances of congenital hydrocephaly and microcephaly." When the cen-

ANENCEPHALY (*McKee and Wells*).
Samaritan Hospital.

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[33] Apert: La Presse médicale, Oct. 28, 1911.

tral nervous system is very poorly developed, the adrenals may be no larger than a lentil. Indeed these organs may be totally absent, as in an anencephalic monster studied by the same author. That the adrenal cortex is mainly at fault in this condition is suggested by the fact that Elliott and Armour[34] witnessed a case in which the cortex was alone atrophic, the medulla of the adrenals and the paraganglia being normal. That this structure is of paramount importance in the development of the organ of mind is obvious. What are the relations between the two?

At the beginning of this chapter, I outlined the process of nutrition of the nerve-cell, including, of course, those of the cortex, as I interpret it. Referring the reader to pages 518, 915, and 946 of the present work for the physiological process involved, I may mention here that, in referring to the secretion of the adrenals, no distinction is made between the cortex and the medulla, it being inferred that, as far as prevailing knowledge will permit, the products of both structures unite in carrying on the functions of the organ.

As regards the relationship between the adrenals and idiocy, the fact that the secretion of these organs is converted into adrenoxidase in the lungs sustains, from my viewpoint, oxidation in the nerve-cell by reacting with its myelin, which contains phosphorus-laden nucleoproteid (supplied with nucleins by the thymus, during development, as we shall see presently), explains the morbid influence of absence or insufficiency of these organs on brain nutrition. While absence of the adrenals or any part of their mechanism inhibits this physiological process sufficiently to arrest the growth of the neurons, thus constituting anencephaly, deficient activity of the adrenals correspondingly restrains their growth, thus leaving the brain in a state of partial development, which in turn entails a correspondingly marked degree of idiocy.

As emphasized by Mierzejewski, the basis of all anatomical lesions in the brains of idiots is an inhibition of the nervous tissues; its origin must be sought either in embryonic life or in pathological lesions produced in early infancy which are the starting point of future anomalies of development. There is no true arrest of development in a morphological and histological respect affecting the brain as a whole, judging from the average post-mortem evidence, but there is a true arrest of development of certain regions of the brain-tissue which may be recognized by the presence of neuroblasts. Some regions, in fact, seem to compensate for these defective areas, for idiots frequently show abnormal aptitudes in certain directions—music, arithmetic, extraordinary memory, etc.—which renders such "freaks" acquisitions for showmen.

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[34] Elliott and Armour: Jour. of Path. and Bact., April, 1911.

The examination of brains of idiots proves that an abundance of gray matter and of nerve-cells may be accompanied by idiocy, but in such cases the system of connections between the convolutions is arrested in its development, and this want of paths of communication and the lack of harmony of development in the different nervous elements render the organ imperfect. In the central nervous system everything depends not on the quantity but on the quality of the elements, and their combinations with each other. The richness of the layer of neuroblasts in the hemispheres of idiots, which indicates true arrest of development of certain parts of the cerebral tissue, undoubtedly produces insufficiency of function of the nervous system and of the manifestations of the intellect. In favorable conditions of nutrition, however, *neuroblasts, may become transformed into elements of a superior order,* that is to say, nerve-cells. In the layer of neuroblasts there are sometimes found polymorphic cells. Thus the neuroblasts, which for a certain time preserve their embryonic forms, and which are in a state of functional lethargy, may, under the influence of a propitious impulse, become transformed into nerve-cells and help in reinforcing the activity of the cerebral functions. It is perhaps in this way that are to be explained the cases of profound and apparently hopeless idiocy in which there sometimes occurs a marked improvement of the intellectual faculties. The idiot seems to wake from a long sleep while, nevertheless, retaining permanently the stamp of his mental infirmity, though in a less marked degree. It is this process of repair which organotherapy tends to promote.

What are the stigmata which enable us to recognize that the adrenals are functionally defective in these cases?

STIGMATA OF DEFICIENT ACTIVITY OF THE ADRENALS AS A WHOLE.—These having been described in full under the caption of Hypoadrenia in the second chapter, they will be only summarized in the present connection. They are briefly: muscular weakness, sensitiveness to cold and cold extremities, low blood-pressure and weak cardiac action and pulse, anorexia, constipation, emaciation, anemia, pallor, and mental torpor, slow intellection or even idiocy if the adrenal deficiency has started *in utero*. As these represent the stigmata of both the medulla and cortex, it becomes a question whether additional light might not be afforded by an analysis of the influence of deficient activity of the adrenal cortex alone.

STIGMATA OF DEFICIENT ACTIVITY OF THE ADRENAL CORTEX.—The prevailing conception of the functions of this structure, as was shown in the first chapter, is that it produces some hormone "which influences, directly or indirectly, somatic and psychic development," experimental and clinical evidence having shown that this influence was exercised mainly upon development of the sexual glands, the body growth and the changes that occur at puberty. These, however, as we shall see, are phenomena due to overactivity of the cortex. When we come to deficiency of this structure, but little may be added to the list of stigmata awakened by deficient activity of the whole gland. Thus its complete removal causes death even if the medullary portion of the adrenals is left, according to Biedl; but other physiologists failed to observe a fatal issue owing doubtless to the presence in the experimental animals of accessory cortical structures well known to exist in the kidneys, ovaries, and other organs. Variot and Pironneau[35] attribute to aplasia of the adrenal cortex a case of senile dwarfism in a girl of 15 years, Gilford's progeria, in which, besides the defective body growth, there was almost universal absence of hair. The presence of osseous dystrophy, however, would point to insufficiency of the thymus, to which I have ascribed progeria.[36] Yet the universal alopecia, which included absence of eyebrows and lashes, suggests concomitant atrophy of the adrenal cortex in the case of Variot and Pironneau, as well as in one reported by Hastings Gilford,[37] in which generalized alopecia was also present, owing to the fact referred to below, that hirsuties is one of the leading stigmata of excessive activity of the adrenal cortex.

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[35] Variot and Pironneau: Clinique Infantile, vol. viii, p. 705, 1910. Quoted by Rand: Boston Medical and Surgical Journal, July 16, 1914.

[36] Sajous: New York Medical Journal, March 20th and April 3, 1915.

All we can add to the preceding list of adrenal stigmata of insufficiency therefore is deficient hair growth, this being controlled by the fact that, as shown below, overactivity of the cortex, such as that produced by tumors, or hypertrophy of this portion of the adrenals, gives rise to overgrowth of hair.

STIGMATA OF EXCESSIVE ACTIVITY OF THE ADRENAL CORTEX.—The clinical phenomena based upon tumors of the cortex can alone be taken as guide in this connection. These depend materially, as to their nature moreover, upon the age of the patient. Thus, a child of 5 years may, as a result of neoplasm in this location, promptly attain the dimensions and physical characteristics of an adult. Bulloch and Sequeira[38] observed a case in a girl of 10 years, whose physical development was that of a woman of 40 years. She began to menstruate at the age of 10, the breasts were fully developed, and the hair about the pubis and axillæ likewise. There was besides, however, pronounced facial hirsuties. She weighed 99 pounds. The autopsy showed a large hypernephroma of the left adrenal. The authors found 11 similar cases in literature, almost all girls. Jump, Beates and Wayne Babcock[39] reported a case, in a girl of 7 years, in whom the abnormal development began, and a growth of hair was noticed first over the pubis, then in the armpits, then over the legs and trunk, and subsequently on the chin and upper lip. She grew rapidly and showed a surprising mental and physical development. Her voice became much deeper and she developed amazing muscular strength, the arms and legs being very muscular. The external genital organs were fully developed, the clitoris, however, being very large and penile in appearance. The uterus and adnexa were found to be infantile, however, in the course of the operation, a large hypernephroma involving the entire right kidney having developed.

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[37] Gilford: Practitioner, August, 1914.

[38] Bulloch and Sequeira: Trans. of Path. Soc. of London, vol. lvi, p. 189, 1905.

[39] Jump, Beates and Babcock: Amer. Jour. Med. Sciences, April, 1914.

The child died three hours after the operative procedure. Of the 17 cases found by the authors in literature, besides their own, all had died before their sixteenth year.

In the male sex the abdominal growth is manifested especially in the direction of marked muscular development and obesity. Guthrie[40] attributes the infant Hercules or Samsons of shows, mythology, and art to examples of this type of disease, just as acromegaly has served as type for Punichinello.

When the cortical tumor occurs later in life, hirsuties is the main phenomenon: the formation of long hairs on the cheeks and chin, the chest, back and limbs of young girls, with perhaps obesity. There is a tendency toward male characteristics, as in the case reported by Jump, Beates and Babcock in a child, the voice becoming deeper, the menses ceasing, and the organs of generation showing progressive atrophy in some. This transformation thus leads to hermaphrodism. Apert[41] refers to 14 cases, in 10 of which the male organs were sufficiently developed to cause them to live as men. The scrotum was empty, and at autopsy the deeper organs were found to possess the female attributes. In the remaining 4 the clitoris was penis-like and the female organs were atrophied. In all of the 10 marked cases either the adrenal cortex was greatly enlarged or large accessory adrenals were present. Auvray and de Pfeffel[42] have also reported a case of hermaphrodism with enormous hypertrophy of the adrenals. According to Glynn[43] hypernephromata are associated with sex abnormalities almost invariably in children and usually in adult females before the menopause.

Summarizing all these facts, the stigmata of *adrenal deficient activity* are as follows:—

1. Muscular weakness and emaciation.

2. Weak heart action and pulse, low blood-pressure, and constipation due to deficient peristalsis, the result in turn of torpor of the intestinal muscular layer.

3. Sensitiveness to cold and cold extremities due to inadequate oxidation and recession of the blood-mass into the splanchnic area.

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[40] Guthrie: British Med. Jour., Sept. 21, 1907.
[41] Apert: *Loc. cit.*
[42] Auvray and de Pfeffel: Société de Chir., May 31, 1911. Quoted by Apert.
[43] Glynn: Quarterly Jour. of Medicine, Jan., 1912.

4. Defective hair growth and pallor owing to inadequate circulation and oxidation in the cutaneous tissues.

5. Mental torpor, slow intellection, or even idiocy where adrenal deficiency is initiated *in utero.*

The presence of these stigmata seem plainly suggestive in the disease treated below, with which, as far as I know, deficiency of the adrenals has not so far been connected by other observers.

AMAUROTIC FAMILY IDIOCY.

This disease, first described by Warren Tay in 1881, has been attributed, by most authors, to some obscure congenital defect. It is uniformly fatal.

Any time between the fifth and tenth month, a normal infant, born at term, will more or less suddenly cease to grow physically and mentally, the physical phenomena consisting mainly in increasing weakness and blindness. The little patient can no longer hold up its head, sit or grasp; and its myasthenia soon becomes so marked that virtual paralysis is suggested. Marked pallor supervenes, due doubtless to atony of the vascular muscles. These phenomena present some kinship with the profound myasthenia of Addison's disease, a fact which suggests failure of the adrenals and of its functional corollary, the chromaffin elements of the sympathetic system, as a feature of the morbid process. The infant also presents evidences of diminished vision: it fails increasingly to notice its mother or nurse, and also objects which, before, attracted its attention. Examination of the fundus, at this time, reveals a picture which has been considered pathognomonic. While atrophy of the optic nerve may be more or less marked, the region of the macula lutea is dark red, and surrounded by a whitish-gray or pearl halo, through which the retinal vessels may be readily seen. Strabismus, nystagmus, and irregularities of the pupils and dysphagia further indicate profound involvement of the muscular system. This is shown also by the profound myasthenia previously mentioned, the child losing increasingly the use of all muscles. What mental development—which may have been quite normal previously—the infant may have shown gradually recedes, the first signs being loss of interest, the torpor in responding to things which before attracted its attention, and indifference concerning its food.

Another suggestive feature in the pathogenesis of this disease is one commonly met in the cerebral palsies of children, viz., periodical convulsions. If the prevailing view that a toxemia underlies the disease is justified, another link with the adrenals asserts itself. In 1891, for example, Abelous and Langlois were led experimentally to conclude that "the adrenals possess the function of neutralizing or destroying toxic substances evolved during muscular labor." Since then, the investigations of Charrin, Oppenheim, of Paris, and others, including myself, have shown that this antitoxic function is exercised in many directions and that poisons of exogenous origin, toxins, inorganic toxics, and drugs, are all neutralized as well as those of muscular origin identified by Langlois as "fatigue poisons" referred to above.

While a toxic of some sort has been incriminated by practically all authors as the cause of amaurotic family idiocy, its nature has not, so far, been identified. Extreme adrenal insufficiency, by permitting the accumulation of certain (probably myogenic) wastes in the blood, seems to afford an explanation. Not only does it correspond clinically in many particulars with the disease in question, but it explains also why the infant is so prone to periodical convulsions. These, under such conditions, occur when the accumulation of poisons reaches a certain limit, the convulsive paroxysm being a protective reaction which brings into abnormal activity all the antitoxic functions of the body, including those exercised by the ductless glands, which, from my viewpoint, and with the digestive glands, as shown later in the present work, form the foundation of the immunizing mechanism in so far as its chemical attributes are concerned. Examination of the adrenals in the autopsies of these cases has unfortunately been superficial. Even under these conditions lesions in these organs have been discerned. Thus, F. Petersen[44] describes his findings in a characteristic case in the following words: "The left suprarenal, pale-yellow color; firm, small cavity in center. Right suprarenal, same."

The genesis of the disease, with deficiency of the adrenals as chief factor of the process, may, quite in keeping with the prevailing view, be traced to a toxemia which the adrenals and other ductless glands are unable to counteract. To refuse these organs immunizing properties, nowadays, is unwarranted. As stated recently by Albahary[45] before the Paris Society of Biology, "As regards neutralizing secretions that the organism can oppose the action of a toxin in general, we know today that this rôle belongs mainly to the ductless glands." This fact established, a toxemia from any cause capable of exhausting these organs or causing hemorrhagic or other organic lesions in them (we have seen in the first chapter that such occur frequently) may thus initiate the disease.

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[44] Petersen: Journal of Mental and Nerv. Dis., July, 1898.

Church,[46] however, states that "none of the alleged toxic factors can be accepted as competent in all instances. As many as 4 cases have been observed in a single family." This is precisely where the prevailing interpretation of the disease is weak: a direct toxemia fails totally to explain one of its characteristic features: that of being a familial disease. This feature is met, however, by the fact that precisely as is the case with other organs, functional debility of any or all ductless glands and their predilection to certain disorders or vulnerability to organic lesions may be transmitted to offspring. An infection capable through its toxins of causing inhibitory lesions in such vulnerable organs—and this may apply as well to any of the ductless glands or to all of them in the same subject—may thus impair sufficiently the nutrition not only of the central nervous system, causing degenerative changes and chromatolysis, but also that of the muscular system at large, the cardiovascular system, etc. That other glands may be involved in the morbid process is suggested by the fact that McKee found lesions in the thymus gland, while Gordon noted enlargement of the thyroid—probably degenerative—in one case and atrophy of the same organ in another. One thing is certain, however: the clinical stigmata coincide with those of adrenal deficiency, and it is probably in these organs that, macroscopically or microscopically, the main causative lesions are to be found.

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[45] Albahary: C.-r. de la Société de Biologie T., vol. lxxiv, No. 4, p. 175, Jan. 31, 1913.

[46] Church: "Nervous and Mental Dis.," by Church and Peterson, p. 250, 1908.

On the whole, available data seem to me to suggest that *amaurotic family idiocy is due primarily to a toxemia, including such as may be caused by a disease toxin, which, by provoking organic lesions in the ductless glands (particularly the most vulnerable of these, the adrenals) when these are congenitally debilitated or vulnerable, so weakens their functions as to inhibit increasingly their power to sustain metabolism and nutrition of the central nervous system, the muscular and cardiovascular systems.*

TREATMENT.—As now interpreted, amaurotic family idiocy is hopeless. That *early recognition of the disease* might check the lethal trend, if the pathogenesis just described proves true, is possible, unless actual destruction of the various ductless glands involved be complete. That such cannot be the case in most instances is self-evident when we recall that a small portion of parenchyma—one-eleventh in the case of the adrenals—will carry on vital functions, and that, moreover, this segment or fraction of organ will become hypertrophied under functional stress. Again, we must bear in mind the presence of the accessory organs some of which may have escaped organic lesions to a degree sufficient to enable them to recover their functions, at least in part.

Not only in so far as the disease in question is concerned, but to prevent the development of any of the forms of idiocy described, any infant who is subjected to any of the infections, particularly diphtheria, meningitis, tonsillitis with rheumatic complications, measles, and scarlet fever, should be closely watched long after convalescence. Unfortunately a condition capable of suggesting the possible development of the disease is usually absent, the process having even progressed *in utero* to such a degree in some instances that the infant is born blind.

As to the measures indicated in the light of the pathogenesis submitted above, they are as much as possible to supply the organic preparation which the stigmata present suggest. If the little patient be still a suckling, the remedy may be administered to the mother, adrenal gland being given in 2-grain doses three times daily and gradually increased to 5 grains. To arrest the degenerative process in the infant, intramuscular injections of infundibular extract, which acts much as does the adrenal principle, may be tried. Pituitrin or "vaporole," an imported preparation, may be employed, diluted in saline solution, and injected into the gluteal muscles after the surface has been carefully asepticized. The dose should be small and adjusted to the age of the infant, any increase being carried out tentatively. Small doses of thymus and thyroid are also indicated to restore the metabolic equipoise in the nerve-cells or facilitate their regeneration.

The diet is an important feature in these cases. It is, in fact, possible that in some instances the maternal milk is found deficient in those agents which, as we shall see, are of primary importance in the development, physical and mental, of the child. When the possibility of this exists the diet of the infant should be reinforced with *fresh-drawn* cows' or goats' milk.

DYSTROPHIA ADIPOSO-GENITALIS.

(Fröhlich's Disease, Adipositas Cerebralis.)

Although the mental symptoms observed in some cases of disease of the pituitary are usually psychasthenic states of a melancholic type, attended, at times, with delusions of persecution, attacks of depression and exaltation, convulsions, etc., cases are occasionally witnessed in which the mental condition is such as to suggest high grade of imbecility in which mental apathy, dullness, and delusions are merged in with the more active symptoms, as observed in a personal case. In another instance, also a case of dystrophia adiposo-genitalis, the patient was irresponsible, childish, and showed a tendency to pilfering. He was unable to acquire knowledge beyond that taught in an elementary school, though showing a marked predilection for music.

Dystrophia adiposo-genitalis, which is a manifestation of deficient activity of the pituitary occurring as the result of an injury, local organic processes such as tumors, etc., is characterized by a marked tendency to obesity, especially about the face (the "moon face" type), the breast, abdomen, and thighs, with sometimes fat pads over the clavicles and under the arms. There is also arrest of development of the genital organs; these remain infantile or atrophy, women ceasing to menstruate when hypopituitarism develops after puberty. The male body assumes a feminine type, especially about the hips. The skin is smooth, though very dry, but sometimes rough. There is absence or scantiness of hair about the pubes and axillæ and trophic disturbances of the nails, the hand being pudgy and the fingers tapering. Symptoms of tumor of the pituitary are usually observed, headache, hemianopsia, blindness, etc.. but in the two cases referred to above pressure signs were altogether absent. The temperature is generally subnormal, 96° to 98° F., and the pulse weak. The blood-pressure is also low in some cases. The development of the bones and ossification of the epiphyses may be retarded and the stature deficient if the case is traceable to the first years of life. If the hypothyroidia be the result of a temporary tumor or of a period of hypertrophy of the gland from any cause capable of increasing for a time its functional activity, the patient may be of normal stature for his age or even exceed it. Under these conditions the acromegalic facies is sometimes clearly discernible. I have seen 2 cases in which it had existed many years, the disorder in the pituitary having doubtless ceased permanently.

In view of the functions I attribute to the pituitary body these symptoms of hypothyroidia are not due to deficiency of a secretion of the organ, but to inadequate activity of the thyroid, adrenals, and thymus, and the resulting vascular dilatation and circulatory torpor in these organs the functions of which the posterior or neural lobe of the pituitary co-ordinates as sympathetic center. Hypopituitarism thus becomes the expression of pluriglandular deficiency, but mild in type, as a rule, death in such cases being due to the lesions caused by the growth in the neighboring cerebral structures. The glandular stigmata in a case of imbecility due to hypopituitarism are as follows:—

1. Subnormal temperature; low blood-pressure; pigmentation (symptoms of deficient activity of the adrenal medulla). Muscular weakness and scanty hair growth; also in a preadolescent case, undeveloped or infantile genital organs (symptoms of deficient activity of the adrenal cortex).

2. Adiposis; smoothness, but in some cases roughness and dryness of skin (symptoms of deficient activity of the thyroid).

3. Undersized growth owing to deficient skeletal development and imperfect ossification of the epiphyses (symptoms in a preadolescent case of deficient activity of the thymus).

TREATMENT.—The medical treatment of these cases can only serve to compensate for the defective activity of the various ductless glands which, from my viewpoint, control the circulation in these organs. In the vast majority of cases the functional activity of the pituitary is compromised by a tumor which, unless removed, compresses and destroys the surrounding tissues and, as previously stated, ultimately causes death. When, therefore, symptoms of pressure appear, such as intense "bursting" headache, visual disorders (due to compression of the optic thälamus), etc., surgical measures are necessary to insure decompression.

At times, however, we witness instances such as the two patients referred to above, in which the pituitary lesion was temporary, though sufficient, when active, to have left permanent nutritional abnormalities such as those recited. In such patients the combined use of the desiccated powders of thyroid 1 grain, pituitary body 3 grains, and thymus gland 2 grains, three times daily for an adolescent, proves very helpful. Pituitary gland alone in large doses—from 3 to 10 grains three times a day—is sometimes sufficient. As I have repeatedly urged, the action of this agent does not prove that it represents that of a secretion, but that the powdered gland contains phosphorus in organic combination owing to the wealth of nerve-cells in the neural lobe—which represents in assimilable form the nucleins produced by the thymus—and also adrenal substance, as shown by the chromaffin test. Watanabe and Crawford[47] also found recently that "pituitary extracts prepared by certain methods give color reactions similar to those given by suprarenal extracts." The activity of pituitary is enhanced, however, when thyroid gland in small doses is administered simultaneously.

THE BACKWARD CHILD.

The great number of these more or less mentally weak children is fortunately beginning to attract serious attention. Particularly is this the case since the investigations of the Russell Sage Foundation in thirty-one American cities have shown that over 20 per cent. of the children in their schools belonged to the "retarded" class, this proportion leaving out of all consideration the 17 per cent. of subjects in whom the retardation was due to late entrance. In other words, approximately one-fifth of all the children in the public schools of the United States are more or less feeble-minded.

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[47] Watanabe and Crawford: Jour. of Pharmacol. and Exper. Therap., Jan., 1914.

DIAGNOSIS AND PATHOGENESIS.—As Barr has well said, "The backward child is not a mental defective but a mental invalid, so to speak, possessed of all his powers, and has the same chance of attaining mental vigor that any sickly child has of being brought to normal health through proper treatment." Thanks to the Binet and Simon method, backward children are now being duly identified, and saved the brutalities which formerly were meted out to them when their defective work and slow progress at school were attributed to laziness, arbitrariness, and stupidity.

The medical diagnosis of these cases requires a careful scrutiny of the many factors which may prevent development of the mind. The stigmata of the various ductless glands described under the preceding headings must be carefully sought. Yet, to attribute all cases of retarded mentality to deficient activity of these organs would be to err as gravely as to ignore them altogether. The nasopharyngeal cavity should be carefully examined for adenoids and hypertrophied tonsils. Not only do they interfere with respiration, both as to intake of oxygen and output of carbon dioxide, but they also compromise the hearing and thus interfere with one of the most important avenues through which the brain receives impressions. Diseased tonsils are detrimental also in that they are frequently the seat of bacterial colonies which, through the toxemia engendered, provoke a protective reaction which, owing to the excess of antibodies produced, exhausts the child (sometimes keeping up a persistent hemolysis with marked anemia, and even chlorosis) and interferes with its physical and, therefore, mental development. Excessive myopia, errors of refraction, any form of markedly defective vision, in fact, is also conducive to mental starvation in exogenous stimuli so necessary to the psychic development of the organ of mind. To remedy adequately these morbid conditions is imperatively necessary; in their presence organotherapy will prove useless.

Treatment.—Before medical treatment is instituted several factors must be taken into account. That insufficient food is a prominent causal feature of backwardness, encountered with special frequency in our public schools, is well known. The functional relationship between the thymus and the brain, maintained through the continuous supply by the former of nucleins which constitute the essential dynamic agent of the cortical cell, accounts for this phenomenon. Organotherapy without an increase of nutritious food in half-starved children is not productive of good, but in some of harm where thyroid is made the sheet anchor of the treatment. It is precisely in such cases that the untoward effects of thyroid treatment and osseous deformities resulting therefrom, especially genu varum, are most frequently observed.

Environment is another factor having considerable influence over the result to be expected from organotherapy. The latter may endow the brain with the potentiality for development, and the neurons reach the maximum state of physical perfection of which they are capable; but if exogenous impressions to develop the psychic functions of the brain are missing, the organ lies dormant and little if any progress is made. In every instance, this phase of the child's every-day life should be carefully scrutinized, and corrected if need be. The company of other children, the schoolroom, where the patient is old enough, and parental efforts to extend the vocabulary and develop understanding, are potent adjuvants when available. Under such conditions marked improvement is often obtained when organotherapy is resorted to to compensate for the deficient hormones in the child's organism.

All the organs of special sense, the child's environment, nutrition and general state of health, especially as regards anemia, tuberculosis, and hereditary syphilis having been fathomed, the condition of the ductless glands must be inquired into, by seeking for the various stigmata described under the preceding headings. Once memorized these signs are readily discerned and the underlying cause of the backwardness, if of glandular origin, is soon established. It is well to bear in mind, however, in many instances the signs of deficiency of any one gland are not easily identified, and that symptom-complex of several glands may appear. Thus a fat, pudgy child, with subnormal temperature, especially in the morning, and showing perhaps fat pads over the clavicles and in the axillæ may prove to be a case of hypothyroidism with secondary deficiency of all the other glands. But this same case may also be one of hypopituitarism. Here, however, infantile genital organs and a feminine build if a boy, and other signs of this condition described under the preceding heading, will appear. If the case be one of hypothyroidia, the use of thyroid gland, 1 grain twice daily, with Blaud's pill of iron 1 grain, and strychnine 1/8 grain, exhibited in a capsule, will soon improve both body and mind by promoting the formation of hemoglobin and the vascular tone. If the pituitary be at fault, pituitary gland powder 2 grains with 1/2 grain of thyroid, also in a capsule, twice daily, will prove beneficial, but not curative.

If the thymus be deficient for the child's age, which is often the case when larval myxedema is present, any mental torpor, the tendency to answer slowly and hesitatingly, is increased and the child's osseous system will most likely show deformities suggesting rickets and looseness of the ligaments. Cutaneous disorders, especially a tendency to warts and eczema, are sometimes observed. Powdered thymus gland, in 5-grain doses, gradually increased to 10 grains, with 1/2 grain of thyroid gland, to each capsule, given in the course of each meal and 2 grains of calcium lactate after meals afford marked improvement in most instances. In some the general health is greatly improved, while the mental deficiency remains the same. In other cases the mental progress is commensurate with that of the body.

A freckled, weak child—weak in the sense of muscular debility and deveolpment, is apt to suffer from hypoadrenia. There is often a history of several children's diseases during which the adrenals, and often the thyroid and thymus, have become the seat of hemorrhagic lesions or have been exhausted functionally, thus retarding development, including that of the cerebrospinal system. Small doses of thyroid, 1/4 grain, with 1 or 2 grains of adrenal gland and 1 grain of iron carbonate, mixed in a capsule, may be given after each meal to a child of 7 years. Sweets will probably be craved; the child should not be deprived of them (some parents being in the habit of forbidding them altogether), as the treatment creates an increased demand for glycogen. Pituitary gland is sometimes more effective than the adrenal, being more lasting; the powder (Armour's) may be given in doses of 2 grains three times a day, iron carbonate 1 grain, and $\frac{1}{10}$ grain thyroid gland.

An important feature of the treatment is to adjust the work allotted to the child to his mental capacity. The Binet-Simon system, or one of its modifications—one of the satisfactory of which is that by Dr. Goddard, of the Vineland (New Jersey) Training School, is employed to establish accurately the degree of intelligence of the backward child. This being determined, the child is placed, where the municipality provides such, in a special class where studies are carefully adjusted to the degree of feeble-mindedness established by the Binet-Simon test in each case. Aided and encouraged, *but not goaded,* a backward child, thus working within the precincts of his abilities, often surprises his teacher by the progress shown, particularly when he is simultaneously treated organotherapeutically.

In the vast majority of communities special classes for backward children are not available. This is, indeed, poor economy, for while instruction and a trade suited to the degree of mentality present will in most instances enable a backward pupil of the poorer classes to earn his or her living, such individuals, unprotected by such instruction, will ultimately become a charge on the community, as a pauper, an idiot, or as a convict. Many years of total and therefore expensive dependence are thus substituted for a few years of inexpensive instruction. All communities capable of supporting a school should provide, singly or collectively, an ungraded class under a teacher specially trained in the management of the feeble-minded. The fact that the higher branches of study are not required simplifies the acquisition of the necessary knowledge by a lower-grade teacher —if temperamentally suited and well endowed with kindness and patience. Such teachers are increasingly in demand, not only for public and private schools, but also for families in which a defective requires competent training. Indeed, an essential feature of the whole question should never be lost sight of, viz., that a backward pupil, when roughly urged to use his brain beyond its powers on the plea of laziness, truancy, etc., may readily be converted into a criminal. Goaded and punished, the child struggles along for a time to keep up with his normal classmates, but discouragement eventually replaces willingness; he becomes irritable and stubborn, and finally leaves school or is dismissed as incorrigible. Such weaklings readily yield to the promptings of evildoers, and not infrequently find their way to the reformatory or prison.

THE PROPHYLAXIS OF MENTAL DEFICIENCY IN CHILDREN.

It has been estimated that several centuries would elapse before eugenics, which aims to improve mankind through heredity, would prove fruitful to any material degree. Dr. Kehoe, superintendent of the Kentucky Institution for Feeble-minded Children, for instance, in extolling the merits of the movement, estimates that four hundred years would elapse before statistics would show much progress. While this estimate is probably excessive, the fact remains that it will take several generations to attain the desired results. In the meantime the number of mental defectives is steadily increasing. The full meaning of this fact imposes itself when we realize that, as stated by Barr, of Elwyn, there are 350,000 avowed mental defectives in the United States, 328,000 of whom are at large "perpetrating unrestrained the defilement of the race." The Russell Sage Foundation has shown, moreover, basing its estimate on a study of the schools of thirty-one American cities, that over one-fifth of all the children in the public schools of the United States belong to the retarded class.

Eugenics being unable to inhibit the propagation of these unfortunates for the time being, some other preventive measure becomes necessary. From my viewpoint, the ductless glands, which, as we have seen, have a controlling influence over the nutrition and development of the body, including the brain, supply the means to this end in respect to the various grades of idiocy and mental backwardness of children.

At the present time, the offspring of feeble-minded parents, though known in advance to be doomed to the same fate, is permitted *in utero* and after birth to follow the evil trend, in virtue it is thought, of transmitted hereditary traits. But the ductless glands tend to elucidate the nature of these traits.

Thus we have witnessed, in all the articles contained in the present and preceding chapters, the intimate functional relationship that exists between the ductless glands and the organ of mind. Not only, as is well known, are such disorders as Addison's disease, exophthalmic goiter, myxedema, acromegaly, etc., attended with abnormal psychic phenomena in a large proportion of instances, but mere deficiencies of functional activity, irrespective of any *active* pathological process in any one of the ductless glands, may so inhibit the nutrition of the brain as to produce the various forms of idiocy and mental backwardness described in the foregoing pages. It is thus apparent that when such diseases are met in the offspring of feeble-minded parents, it must have been through the inheritance of deficient ductless glands from the latter or through them from ancestors.

This imposes the necessity of showing that diseases, intoxications and other causes of idiocy are capable of provoking lesions in the ductless glands of the parents or ancestors. Ample evidence to this effect is available. Alcohol, gout, lead poisoning and infectious diseases all, we now know, impair the functional activity of the ductless glands either by provoking organic lesions in them or in their nervous supply or exhausting them functionally. Syphilis has been shown to do so by Fournier, Lacaze, Sirena, Furst, Gulecke, Marfan and others. Tuberculosis is a notorious offender in this connection, Addison's disease, in fact, being in most instances due to tuberculosis of the adrenals; but, as Rénon[48] states, moreover, all the ductless glands, the thyroid, adrenals, pituitary, etc., are the seat of degenerative changes in tuberculosis. Sabourin[49] has recently emphasized the frequent concurrence of hyperthyroidism with the latter disease—a sign that it is causing excessive functional activity of the thyroid. Rheumatism is so frequently accompanied by disorders of the thyroid that the connection is now generally recognized. Alcohol is also a common offender; the microphotograph opposite page 1332 in the second volume shows that even the pituitary body may become the seat of fibrous degeneration, which means, in the light of my interpretation of the function of this organ, insufficiency of all the major ductless glands, the circulation of which it governs. These few examples could be multiplied almost indefinitely. They will suffice to show, however, how exposed are these organs to functional deterioration by the very pathogenic factors in forbears to which idiocy in their offspring has been traced.

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[48] Rénon: La Tribune médicale, July, 1911.

[49] Sabourin: Archives générales de méd., Jan., 1914.

That so many different morbid conditions should be able to provoke mental deficiency is readily explained by the fact that *any disease capable of injuring the ductless glands sufficiently to inhibit their functional activity, or inherited insufficiency of these organs, impairs the development and functions of the brain, by reducing the supply of secretions this organ requires to carry on these physiological processes.* We shall see in a succeeding chapter that the adrenal secretion circulates in the nerve-cell. This fact, which I pointed out in the first edition of the present work in 1903, was sustained by the experiments of Lichwitz[50] in 1908. The thyroid secretion being necessary, as we have seen, to co-operate with the adrenal secretion to carry on oxidation, the thymus supplying the nucleins which are oxidized, it follows that deficiency of these glandular products must entail deficient nutrition of the cerebral cells and correspondingly defective mental power.

Under these conditions, a pregnant defective fails to supply her fetus the ductless gland secretions it requires. Why permit this? Why seal the child's fate through inactivity? It is my firm belief that, with what knowledge we have of the ductless glands even at the present time, *we could diminish the chances of such children developing into mental defectives by supplying them, through the intermediary of their defective mothers, and after birth through their food, the secretions they lack to complete their development.*

This opinion is based on the undoubted influence of the various ductless glands upon every phase of the process of reproduction. This is so well known that I will submit but a fraction of the testimony available to that effect. As stated by Telford Smith: "The thyroid gland of the mother increases during pregnancy and remains enlarged during lactation, showing," adds this author, "that it is connected with fœtal development."

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[50] Lichwitz: Arch. f. exper. Pathol. u. Pharm., Bd. 58, Hft. 3 u. 4, S. 221, 1908.

The adrenals are also known to be enlarged and overactive. Neu, moreover, found that the proportion of adrenalin in the blood corresponded quantitatively with the activity of the gestative process, including the period of pregnancy. As to the pituitary, it was found to be overactive during pregnancy by Comte Launois and Mulon and others. Swale Vincent states, in fact, that it may enlarge to two or three times its normal size. That the thymus is concerned with the development of the offspring both during uterine life and after birth needs hardly to be emphasized. We now know that its influence bears mainly upon the osseous and cerebrospinal systems.

As to the effects on the offspring of defective ductless glands in the parents, they may be illustrated by the statement of Hertoghe that "where the mother, for instance, has at her disposal a sufficient store of thyroid secretion the child does well, whereas if there is thyroid insufficiency, especially if there is a history of inherited disease, alcoholism, etc., the child will probably be a myxedematous cretin. . . . Should the maternal taint be slight, the child will be merely backward." That the deficiency of thyroid of a defective mother of the type referred to by Hertoghe influences her offspring is well shown by a case of Mosse's,[51] in which a goitrous, feeble-minded mother gave birth to a puny, goitrous infant. The child being breast-fed, thyroid gland was administered to the mother, with considerable benefit to her, but with early disappearance of the goiter in the child, whose health, moreover, became excellent. This was evidently due to the action of the thyroid gland acting through her milk, for Bramwell[52] observed a case in which hyperthyroidism was caused in an infant by administering thyroid gland to its mother, who nursed it. Everyone knows, moreover, that both thyroid gland and pituitary markedly activate lactation.

On the whole, the intimate relationship between the ductless glands and everything that concerns reproduction, the great relative size of these organs in the product of conception, and the teachings of practical experience in organotherapy, all tend to indicate that *whenever the father or mother is a mental*

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[51] Mosse: Bulletin de l'Acad. de Méd. de Paris, April 12, 1898.

[52] Bramwell: London Lancet, p. 692, 1898.

defective or one or both parents show any sign of deficient activity of one or more ductless glands, or whose history includes syphilis, epilepsy, tuberculosis, or chronic alcoholism, organotherapy should be instituted as soon as pregnancy is recognized.

PROPHYLACTIC TREATMENT.—To determine the course to follow, the stigmata of deficiency of each of the major ductless glands should be ascertained. In most cases the signs of deficiency of one of the glands predominate, and, such being the case, the use of that gland therapeutically as dominant constituent of the combination employed will procure the better results. These signs have been given in the foregoing articles of this chapter (see pages 279, 288, 300, 302, and 308), to which the reader is referred. If the myxedematous type prevail, thyroid gland should be the dominant constituent; if the Mongolian, the thymus, etc., the other organic products being given with it to provide for the developmental equipoise of the fetus, deficiency of one gland entailing deficient activity of the others. As we have seen also, all the ductless glands may be organically diseased or deficient in the parent, in tuberculosis for instance; in such a case the stigmata of several glands may appear, though not prominently. For the diagnosis and treatment of such cases, the general lines advocated for backward children (see page 311) will serve, the doses being increased to those suited for an adult. Additional hints are given at the end of the present article.

The pregnant mother having been carefully treated organotherapeutically according to the stigmata she presents, the infant will be supplied *in utero* with the secretions required to build up, not only its nervous elements, but also its osseous, muscular, cardiovascular, cutaneous and other systems. It will also be prepared to develop normally after birth, provided the treatment be continued. This may be done, as previously stated, either through the maternal milk or, if the infant be fed artificially, by adding the organic agents to its milk. Besides protecting the child, organotherapy protects the mother against renal disorders, eclampsia, etc., by increasing the antitoxic power of the blood and thus preventing the accumulation of toxic wastes which cause these disorders.

The continuation of prophylactic treatment through the maternal milk after birth will do more than approximately restore the developmental balances, physical and psychic, of the child; it will serve to protect it against disease. Indeed, the milk of a normal woman does more than feed her suckling; it is now known to protect the infant against infection by means of ferments which correspond in their physicochemical properties with those of the ductless glands. In a mentally defective woman, however, the probability (shown by autopsies) that one or more glands may be defective gives her milk a doubtful character; hence the need of continuing the use of organic products. Cows' milk contains all the defensive ferments referred to, but, unless it can be administered absolutely fresh, its protective properties disappear, the milk then becoming an excellent culture medium for pathogenic organisms. Cows' or goats' milk fed to the infant immediately after being drawn from the udder, and not Pasteurized—since this measure destroys some of the ferments—will alone sustain the effects of the treatment begun *in utero*. Even under these conditions, however, the use of organic products with the milk is advisable, the tendency of all children thus treated being to recede unless this is done, at least until their own ductless glands acquire sufficient power to carry on their functions normally. The results in these little patients, especially when, as is the case in most instances, the predominant stigmata are of thyroid origin, are sometimes surprising.

Another feature which the teachings of clinical experience have emphasized is that the younger the child the greater are the chances of restoring its psychic functions, if these have failed to develop. After the first few years of life, some improvement is obtained from organotherapy, but this is far from being ideal. This indicates plainly that *the development of all infants should be closely watched by the family physician, particularly if the family history is tainted, the physical and mental growth being compared with that required by normal standards. Any departure from the latter should be the signal for a careful examination of the organs of special sense of the child, the manner in which it is fed, etc., and if its condition cannot be accounted for through these factors and removed, organotherapy should be instituted.*

The thousands of purely functional defectives which the country contains are, as we have seen, judging from personal cases, the children of parents in whom, in most instances, clearly defined stigmata cannot be discerned. This means that any infant may become a defective unless its development be closely watched by the attending physician. At the present time, the evil trend is discovered too late to save the child's mind. Were every infant closely watched from birth, and its development, physical and mental, compared with that of a normal child (standard tables being available in most works on pediatrics), timely treatment could be instituted and a large proportion of them redeemed. In addition to the use of organic products indicated by the stigmata discovered, the special senses should be cultivated, external impressions being all important factors in psychic development. It should be remembered also that disorders of the eyes, ears, nose, and nasopharynx may be the underlying cause of defective mental development in infants.

All this bears only, of course, upon the defectives clearly traceable to inherited taints, all types of idiocy up to and including the backward child of our schools being meant. As in insanity in general, two great classes of idiocy are recognized: the organic, in which traumatism, hemorrhage, gummata, etc., have caused more or less localized lesions of brain-tissue and compromised psychic functions; and the functional, in which no organic lesions are present to account for the mental defect. It is in this functional type that heredity finds its greatest field. Unfortunately, as is well known, a large proportion of idiots show, *post mortem*, lesions of the brain such as sclerosis, atrophy, softening, etc., which no longer are cultivable soils. Yet, distinct improvement is often obtainable even in such cases. This is because the degenerated areas are seldom bilateral and the corresponding areas on the opposite side of the brain can thus be made, through improved nutrition and oxidation, to compensate to a remarkable extent, sometimes, for the shortcomings of the functionless areas. Even these areas are sometimes subject to improvement, Cattani, Klebs and others having shown that regeneration occurs occasionally when the lesions are comparatively slight and of recent formation.

Organic lesions of the ductless glands of the infant may also complicate the situation. Both these and the brain lesions may be caused by an accumulation of toxic wastes during the pregnancy—the same intermediate wastes which cause nephritis and puerperal convulsions. The intense vascular tension awakened gives rise to hemorrhagic foci in the brain and ductless glands, with resulting impairment of the organ of mind. This emphasizes anew the commanding importance of the advice of obstetricians to watch the kidneys closely during pregnancy. The most frequent sources of lesions of the ductless glands, however, are the diseases of childhood. It is only a few years since some textbooks of practice condemned precautions to avoid measles on the plea that the sooner it was over the better for the child! But we know today how pernicious was such advice. Not a small proportion of the cases of idiocy we meet date from some children's disease during which hemorrhage into the ductless glands compromised their functional integrity sufficiently to arrest cerebral development.

Here again, however, pessimism as to results is not warranted if the child is seen early enough. A characteristic feature of the ductless glands is their tendency to hypertrophy when the normal glandular tissue left after local lesions is sufficient to carry on their functions. Thus, one-eleventh of the adrenals suffices to insure this and one-fifth of the thyroid, also, provided the parathyroids are unharmed. If, however, what remains of the ductless glands of the child is not sufficient to sustain adequately general nutrition and brain development, organotherapy will serve to compensate for the glandular deficiency. We recognize these cases by the fact that they soon recede, after distinct improvement, as soon as the remedy is stopped and resume progress when the treatment is restored. But perseverance will elicit the fact that smaller doses will meet the needs of the cases after a time—evidence to the effect that the ductless glands themselves are increasingly meeting the demands of the organism. If the little patient is young enough, the time may come when no treatment will be required.

Of the organic agents indicated in these cases, my preference has been so far for the desiccated gland in powder form. Experience has shown that, where simplicity prevails in the use of these agents, the patients tend better to persist in their use. Again, powdered glands of a different kind can be conveniently combined and given to adults in capsules or mixed with the milk given to infants, unless they are breast-fed, when the gland is administered to the mother, her milk, we have seen, transferring the remedy to the suckling. In some instances, the unpleasant taste given to the milk causes the child to refuse it. Then a fluid preparation may be given when such is available.

In cases of maternal hypothyroidism, 1 grain of desiccated thyroid gland may be given three times a day, during meals. Mental defectives require somewhat larger doses. For infants the dose must, of course, vary with the age of the little patient; 1/12 grain is a suitable dose for an infant 1 month old; this may be increased by the same quantity for each month; a 2-month-old infant being given 1/6 grain, etc. As a rule, a year-old baby stands 1 grain daily without trouble. Adrenal gland may be given to adults in whom adrenal stigmata are present, in 2-grain doses, gradually increased to 5 grains unless constipation follow its use. Pituitary gland powder, 2 grains three times daily, is more efficacious. For the infants of such subjects pituitrin—a liquid extract of the infundibular portion of the pituitary—in drop doses in the milk to begin with, and increased as required, is more effective than any preparation of the adrenals. Thymus gland may be given in from 5- to 15-grain doses to the mother and 1-grain doses to the infant, gradually increased to the point of tolerance. This organic product is not always reliable and it is sometimes necessary to use the "neck sweetbread" of butchers instead. The compound syrup of hypophosphites is helpful when given with thymus gland. Often, a combination of these agents will doubtless hasten improvement. All cases in which organotherapy is resorted to must be watched closely to obviate untoward effects. The dosage must be adjusted to each case, susceptibilities to organic agents, and notably thyroid, varying considerably.

DEVELOPMENT OF THE SENSES.—Reference has been made to the importance of the senses, most of which are developed at birth, in the psychic development of the infant. When any of them show distinct evidence of lagging behind, measures, some of which are submitted, should be taken to favor their development.

Hearing.—Even in the infant, the auditory apparatus and the word-hearing center which constitute the main cerebral mechanism of language are highly receptive. We have, therefore, in the apparently meaningless terms of endearment and praise, the prattle of other children, the cradle songs, and other forms of music, especially instrumental music, frequently repeated simple words, particularly if connected with some craving which the child's instinct will inspire, such as that for food, including the breast or bottle, etc., as many sources of stimulation which co-operate efficiently with the organotherapeutic measures adopted. With patience and perseverance and much repetition—virtues extolled in this class of cases by the late Edouard Séguin—unexpected results are sometimes attained.

Vision.—A careful examination by an ophthalmologist having shown that no organic disease of the visual apparatus exists to account for the apparent blindness, or defective vision, and appropriate medication having been instituted, resort should be had to out-of-door life, and to various glittering objects to excite the retina and through it the visual apparatus,—first, as the vision is weakened by bandages over the eyes or the dark rooms, so can it be stimulated by daylight. The baby coach is of great aid in this connection, its hood serving to shade the eyes, without interfering with the entrance of the surrounding bright light through the retina. The retinal muscles and those of accommodation and motion are also stimulated out-of-doors through the many factors, distance, variegated coloring, moving objects, etc., which a nursery does not supply. A glittering call-bell, several bright teaspoons tied together in such a way as to cause them to jingle when shaken, a shining baby rattle, etc., will enlist the help of the sense of hearing, and afford the mother a clue to the progress made as regards directed vision. The distressing vagueness so characteristic of these little patients when they attempt to see anything will at first breed discouragement in the attendant, but patience, aided by appropriate treatment—direct or transmaternal—and the steady development of attention and interest ultimately afford reward for patient efforts.

Smell and Taste.—One of the leading features in the recognition of mental deficiency early in a child's life is that where organic lesions do not exist; the nervous system, which normally would be in process of rapid development, responds with greater activity than later to the influence of remedies, especially organic preparations which actually nourish the nerve-cell and sustain its metabolism. The olfactory and gustatory apparatus thus develop more rapidly than in the older child, in whom the morbid process is more firmly established and therefore more resistant.

Important in this connection is the fact that where any or all the special senses show any marked degree of deficiency, the thymic nucleins should be supplemented by a preparation of phosphorus. Of special value in this connection is the official syrup of hypophosphites, which also contains a small dose of strychnine, 1/12-grain to the drachm of syrup.

Cutaneous Sensibility.—The usual means to develop touch —smooth and rough surfaces, buttoning, warm and cold surfaces, etc., used for older children—are useless for infants. These require measures which excite the entire surface. In some mental defectives the temperature sense is so obtunded that a hot object, which normally causes rapid withdrawal of the hand in contact with it, fails even to attract their attention. And yet these same children, who will appear dull, sleepy and torpid in cold weather, will, during warm weather or under the influence of a mild febrile process, become unusually bright and active. Why is this? It is due, from my viewpoint, to a physical phenomenon the far-reaching importance of which I have long urged, viz., that *while ferments carry on metabolism in all tissues, the temperature to which these ferments are subjected in the tissue-cells governs the rate of metabolism in those cells.* Hence, warmth applied to the surface enhances metabolism and, therefore, the vital activities of the entire organism. We therefore have, in hot baths twice daily, or, in heliotherapy, exposing the nude body to solar heat during prolonged periods, as is now successfully done in the treatment of osseous and glandular tuberculosis, potent aids in the treatment of these cases. Indeed, by supplying the infant the glandular substances which carry on its vital functions and simultaneously heat to raise the activity of these functions to their highest potential, we antagonize precisely the slowness of metabolism in all tissues —including the cerebrospinal system—to which the hereditary forms of idiocy and mental backness are due.

CHAPTER VII.

DISORDERS DUE TO DYSFUNCTION OF THE INTERNAL SECRETIONS.

DEMENTIA PRÆCOX.

ALTHOUGH dementia præcox represents about twenty-five per cent. of the admittances to all insane asylums, fifty per cent., the figure given by Bayard Holmes as representing the proportion of cases in Illinois, is probably nearer the truth for the country at large. This figure may certainly be adopted as the probable one if to the asylum cases we add those in private institutions and those at their own homes, including the thousands on the border line which either have not as yet been recognized as victims of the disease, or belong to the simpler group of "apathetics" and "indifferents." In other words, one-half of our insane of both sexes are recruited from adolescents. And this does not include another large class, that of the feeble-minded—an important distinction, for the candidate for dementia præcox is not infrequently unusually intelligent, and finds his or her mental doom in overstudy.

The gravity of the harm done by this dread malady is further emphasized by the fact that when it occurs among the poor and in environments where immorality reigns, it breeds the paranoiac crank, the irretrievable criminal, the vagrant, the prostitute, etc. It is hardly necessary to dwell on the importance of any effort to stem such a tide of misfortune and iniquity. It is gratifying also to realize how widespread have been the efforts in the same direction of late. Some of these efforts are already beginning to bear fruit, and, if the many phases of the problem continue to be studied diligently, and if the general practitioner, who is first consulted in practically every instance, will familiarize himself with the early clinical picture of these cases and institute both prophylactic and remedial measures, the gloomy prognosis may be replaced by one affording at least some encouragement for the future.

A few years ago, Bayard Holmes,[1] criticizing the purely psychogenic doctrine of the disease, wrote: "One might as well talk to the alienist of death and its prevention as of dementia præcox and its cure. To the psychogenist, dementia præcox is the result of 'twisted idea' of some sexual nature which upsets the whole organism. It disturbs adaptability, destroys emotion, paralyzes volition and precipitates a physical and mental degeneration and dissolution. The 15,000 youths of high school age who go into the madhouses of our continental empire every year, leave all hope behind. During the first year of incarceration they have a very high death rate, almost 100 per 1000; but if they survive this critical period, they live about seven years in custody, and 54 per cent. of these die of tuberculosis." . . . . "Another 20 per cent. become mute, inactive, catatonic, 'untidy' and curl up polluted every day in their own offal, to die of starvation, bed-sores and intercurrent disease." Commenting then upon the virtual impotence of alienists as regards any curative treatment of the disease, he describes what may prove to be a new era in this respect.

This new era he connects with what he terms "a most remarkable phenomenon" discovered in 1912 by the Swiss biochemist Abderhalden,[2] *viz.*, that toxic albumins of endogenous or exogenous origin provoke in the blood a defensive reaction consisting in the reduction of these toxic albumins to a peptonoid or soluble form which enables them to be readily excreted by the kidneys or liver. The active agents in this process Abderhalden termed "defensive ferments" (to which reference will be made in the next chapter) which he deemed similar "to those secreted by the digestive glands in the intestinal canal." Those who are familiar with my labors, are aware of the fact that long before Abderhalden, I[3] published in the present work (see also next chapter) similar conclusions to his, concerning the rôle of digestive ferments and certain ductless glands in cellular metabolism and defensive functions, differing only from his independent observations in that *certain* leucocytes were factors in the process, The fact that from two independent directions, identical results should be obtained, indicates the strength of the position as a working basis. The Abderhalden reaction itself, which can be performed in the test-tube, is of course familiar to everyone. Now this reaction has shown distinctly that the various ductless glands, including the sex glands, were the seat in dementia præcox, of abnormal activity, the thyroid for instance, showing the characteristic picture of hyperthyroidia or exophthalmic goiter.

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[1] Bayard Holmes: Medical Fortnightly, Jan. 26, 1914.
[2] Abderhalden: "Defensive Ferments," 3d ed., 1914.
[3] Sajous: "Internal Secretions and the Principles of Medicine," vol. i, pp. 608 to 745; vol. ii, pp. 885 to 907, 1907.

Various authors had tentatively suggested that the ductless glands had something to do with dementia præcox, some suggesting overactivity, others to deficient activity of one or more glands, without working out the nature of the process involved. On the other hand, several authorities, notably Régis, Kraepelin, and Dercum, have attributed dementia præcox to some form of toxemia. We shall see presently both the nature of the endocrine process and the source of the pathogenic toxin.

Very suggestive also was the fact demonstrated by the Abderhalden reaction, that the various ductless glands were the seat in two-thirds of the cases of dementia præcox, of degenerative processes. The existence of such lesions is well shown by eight cases carefully examined post-mortem by Dercum and Ellis,[4] who conclude their valuable study with the following statement: "Without attempting an interpretation of the histological conditions—a matter of extreme difficulty in the present state of our knowledge—we are at least justified in the conclusion that in our cases there was in all probability a disturbance of what Sajous has called the 'adrenal system,' *i.e.*, of the chain made up of the pituitary, the thyroid and the adrenals. Especially was change noted—*e.g.*, striking departures in weight—in the thyroid and adrenals. Now Sajous has pointed out that in tuberculosis there is an inadequacy of this adrenal system and the thought naturally suggests itself that these eight patients suffered from dementia præcox for the same reason that they subsequently suffered from tuberculosis; that is because of an inadequacy or abnormality of their adrenal systems. It is rather a remarkable fact that the almost universal cause of death in dementia præcox is tuberculosis and if the feebleness of resistance to the tubercle bacillus is due to a fault of the adrenal system, we have reason to infer that this fault pre-existed and that it is one of the factors in the makeup—the morphology—of dementia præcox."

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[4] Dercum and Ellis: Jour. of Nerv. and Mental Dis., May, 1913.

This conception is of value in the sense that it gives us, poised on sound histological facts, the culminating or terminal feature of dementia præcox, *e.g.*, breaking down of the ductless glands, with tuberculosis as result, because by provoking degeneration of these organs, the disease or its causes reduced the efficiency of the systemic defensive mechanism and made the body vulnerable to infection. It is not, with this terminal stage of the disease, a "feebleness of resistance" due to faulty endocrinic activity, however, that we have to deal, but with a gradual destruction, by the disease itself or its causes, of endocrinic efficiency. But how can dementia præcox or its causes bring this about? Herein lies, it seems to me, a fundamental feature of the disease and a clue to its rational interpretation.

In order to make this clear it is necessary to review, though very briefly, the functions of the various ductless glands involved as I have interpreted them.

We have seen in earlier chapters that it is clearly through the adrenal secretion that the venous blood is converted into arterial blood and that the life of every cell, including nerve cells, is sustained. Another function of the adrenals of importance in this connection however, is that concerned with the destruction of various poisons, including toxic wastes, pointed out by Albanese, Abelous and Langlois, and sustained by others since. We have but to recall the vulnerability of cases of Addison's disease and the various forms of adrenal insufficiency to intercurrent infections to realize the importance of this defensive rôle. Now these two functions, respiratory and antitoxic, bear directly, as we shall see later, upon the pathology of dementia præcox, for while, as will be shown farther on in this work, adrenalin laden—or better, oxyhæmoglobin laden—plasma circulates (as does tetanotoxin), in the axis-cylinders, cell-body and fibrils of nerve cells, the antitoxic virtues of this plasma are also brought into play through the presence therein of the adrenal principle.

As to the thyroid, I need but recall its paramount rôle in metabolism, which in Kendall's words: "are so great that practically every cell within the animal organism is changed. The effects are felt throughout the nervous system and the circulatory system; the rate of metabolism is enormously increased." There is one feature of the process, however, that is also of cardinal importance in dementia præcox besides its influence on the nervous system—through which it circulates likewise from my viewpoint—and that is the marked influence of thyroid on the catabolic phase of metabolism. This is well shown by its action as an antifat, so abused at one time. It first attacks the fats, then the other tissues when administered in excessive quantities and the body steadily dwindles down until dangerous cardiac symptoms appear.

But this stimulating action on catabolism has its good sides and this is a third feature bearing directly upon dementia præcox. Briefly, the same action through which the thyroid secretion breaks down metabolic wastes causes it also to break down bacteria, toxins, and other organic poisons. It thus becomes a defensive action. We have seen that the thyroid hormone in this connection is in reality what Sir Almroth E. Wright had termed opsonin and the sensitizing agent in our body fluids, both the plasma and phagocytes. This view has also been confirmed. Léopold-Levi and H. de Rothschild,[8] for instance, writes: "Sajous has attributed, among the functions of the thyroid body, a rôle to the latter which he assimilates to that of opsonins and autoantitoxins. More recently, Fassin of the Bacteriological Institute of Liége, and Stepanoff and Marbé of the Pasteur Institute of Paris, have confirmed on their side the influence of the thyroid on the blood's asset in alexins and opsonins." Others have also adduced evidence showing that the thyroid product influenced favorably autointoxications and infections of various kinds.

The thymus, we have also seen, does not, as generally taught, disappear at puberty. It begins to diminish rapidly in size at that time and by the twenty-fifth year has atrophied to about one-fifth of its former dimensions, retaining a relative proportion of functional parenchyma. Thence on it disappears very slowly until about the age of sixty, when but a small remnant, containing usually parenchyma, is left.

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[8] Léopold-Lévi and H. de Rothschild: "Physiopathol. of the Thyroid Gland," vol. ii.

Several salient physiological facts connect the thymus with dementia præcox. In the first place, absence of the thymus is almost constant in noncretinic idiots, 302 times in 408 cases examined post-mortem by Morel,[6] 28 times in 28 cases examined similarly by Bourneville. In the second place, though classed as a lymph gland, the thymus is five times richer in nucleinates than the latter; and it is these nucleinates (which contain 3.7 per cent. of phosphorus) that the thymus, through its migrating cells, the thymocytes, supplies to both the nervous system at large, including the brain, and the bones. Hence my conclusion[7] many years ago, that the function of the thymus was to supply the excess of phosphorus in organic combination that the body requires during the development of the child. It is, in other words, the fundamental ground substance for the fats (the myelin, lecithin, etc., and nucleins) of nerve cells. The third and last feature which bears directly upon dementia præcox is also often overlooked, *viz.*, that the thymus depends for its efficiency upon adequate feeding and upon conservation of its supply of nucleinates to preserve the functional integrity of the tissues it supplies. We shall see presently the bearing of this phase of the question in point.

With these few physiological data as basis, let us try to unravel some of the prevailing obscurities.

That a toxæmia is an exciting cause of dementia præcox is now accepted by many observers. Severe infections, pregnancy, the puerperium, the climacteric, severe mental stress, traumatisms, excessive exertion, fecal stasis and autointoxication, are some of the causes of toxæmia found in the histories of the cases. A suggestive feature in this connection is that this list corresponds exactly with that which endocrinologists have worked out as the leading etiological factors of hyperthyroidia and its most advanced type, Graves's disease. In fact, everything tends to show that the only differences between these two disorders lie in the facts that *while dementia præcox occurs in*

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[6] Morel: Paris Med., iv, 161, 1914.

[7] Sajous: "Internal Secretions and the Principles of Medicine," 7th ed., p. [illegible], 1916.

individuals predisposed in the majority of instances by heredity to psychoses, and possessed of a normal thyroid but a deficient thymus; Graves's disease occurs in subjects who are predisposed to that disease through heredity or in whom acquired structural lesions in the thyroid have enfeebled its secreting power, thus rendering excessive (and therefore pathological) activity of its secreting elements necessary.

Etiologically, simple goiter also shows kinship with both dementia præcox and exophthalmic goiter for, as shown by the painstaking labors of Major McCarrison, of the Indian Medical Service, an undetermined variety of colon bacillus, derived from fecal matter ingested with water, is undoubtedly causative of this condition, while my own observations in Switzerland, where fecal matter is generally used to fertilize vegetable patches, and indirectly contaminates wells, have led me to ascribe most cases in endemic districts to this cause. Familiar also is the goiter of adolescents so common in our schools, another point of resemblance with dementia præcox. Again, many years ago W. Hanna Thomson in a campaign against a relationship between the thyroid and exophthalmic goiter, attributed this disease entirely to a toxæmia of intestinal origin, recommending purgation and appropriate diet to cure it.

In dementia præcox, the same series of events occur. The intestinal tract is undoubtedly a prominent offender. As worked out by Bayard Holmes and his associates,[8] a toxin is produced by the growth of organisms of the colon group upon unassimilated food proteins either in the cecum, owing to prolonged stasis therein or beyond the ileocecal valve. The cecal stasis is such, he states, that as observed by fluoroscopy and a progressive barium meal, the latter may be found to remain (thus typifying the fecal mass) from 54 hours to 3 weeks in these intestinal areas. In one of my own patients, a 48-hour fecal stasis, probably with a stationary mass, observed with barium meals and repeated x-rays, sufficed to provoke a severe form of the disease.

In this particular instance, I was able to verify the truth of the following statements as regards "remarkable improvement"

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[8] Bayard Holmes: Trans. Research Lab. of Psychop. Hosp. Cook Co. Hosp., Chicago, *Ibid*, p. 283, 1912.

(the patient has now been well two years) also by Bayard Holmes, who refers to: "Remarkable improvement and even recovery in few patients treated by appendicostomy and protracted irrigation of the cecum and colon with large quantities of water. By this direct and positive method," he states, "the attempt has been made to arrest the production of toxic amins in the cecum and diminish the amount of the toxic substances absorbed." In the personal case referred to above the appendix had been removed some time before; cecostomy was therefore performed for me by Professor Ernest Laplace, and irrigation of the cecum and colon carried out through a rubber catheter introduced into and kept in the cecal opening. Instead of using plain water, however, for the irrigations, I advocated the use of warm saline solution—much of which was retained—my reasons for the change being as follows:

Professor N. Ishida,[9] of the Nagasaki Medical College, recalling the fact that Kraepelin[10] had found experimentally that sodium chloride infusions caused "an increased feeling of hunger and thirst accompanied by a regular improvement of the general health," tried their use in dementia præcox, using a 0.09 per cent. solution intravenously where possible, in quantities ranging from 300 to 1000 grammes repeated, where this was done on an average of four cases about every twelve days or three times out of the ten cases studied, and, in one instance, in thirty-nine days. In one case, there was no change excepting a temporary increase in interest; in three there was lasting improvement; in four, remissions lasting from one to three and one-half months; in one, a remission which may have been spontaneous; in one, sufficient improvement to warrant discharge. Another series of fifteen cases treated in the same way, L. V. Guthrie[11] gave the following results: 10 cases, very unclean before treatment, were improved in this respect. In 8 cases, there was an awakening in interest in work, directly following the treatment, and in 7 of these cases, this has continued. Remissions occurred in 6 of the 15 cases but these improved again on reinjection of the solution; 7 cases have greatly improved without remission. One apparent cure, without remission since treatment was commenced 5½ months ago. Second apparent cure without remission for three months. This case has put on twenty-five pounds in weight and improved mentally to a surprising degree. All 15 cases showed increase in appetite for food and all gained flesh."

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[9] N. Ishida: Amer. Jour. of Insanity, vol. 73, p. 543, 1916-17.
[10] Kraepelin: Psychiatrie, 8th ed., vol. i, p. [illegible].
[11] L. V. Guthrie: W. Va. Med. Jour., Dec., 1917.

A feature to which special attention must be drawn is that Ishida observed following the first infusion in some cases, what he terms "a fever of unknown origin" ranging from 39.6° to as high as 40.5° C., followed by excitement in two instances, which may, he thinks, have been "the result of defective sterilizing methods." "Yet," he states, "the occurrence of fever in some instances after the infusion is not, without significance, since the mental status of patients with endogenous dementia has often been noticed to have improved after the occurrence of fever."

In the second volume of the present work I stated[12] referring to sodium chloride: "When the supply is inadequate, all the functions are hampered, since it is the solvent of adrenoxidase (serum globulin.) By holding the latter in solution it insures its free circulation as a constituent of the plasma in all vessels down to the minutest capillary networks distributed to cellular elements, including those of the nervous system: The axis-cylinders and other neuro-fibrils, the networks of neurons, their dendrites, etc. This also enables the adrenoxidase-laden plasma to transude freely through the capillary walls in order to reach the tissue-cells, *i.e.*, to carry on the life process. The free osmotic properties which the lymph in the tissue-spaces also owes to sodium chloride insures another important function, viz., that of sweeping away by the lymph-current of all wastes derived from the cell." The fever referred to by Ishida thus finds a normal explanation: the *defensive properties of the blood plasma and its cells being enhanced by the saline solution, an exacerbation of antitoxic activity,* i.e., *fever resulted,* followed by improvement. In other words, what benefit was derived from this method—and I have seen improvement result in other cases from large colonic irrigation with saline solution—was due to the general destruction of the causative toxics and a temporary arrest of their injurious effects upon the cerebral cells. To this must be added a similar action with improvement of osmosis in all tissues including the ductless glands, thus facilitating the liberation of the secretions of the latter. This means restoration of general metabolic activity besides the resumption of antitoxic power—salient functions, we have seen, of the thyroid and adrenals.

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[12] Sajous: "Internal Secretions and the Principles of Medicine," vol. II, p. 1369, 1st ed., 1903.

A toxæmia, demonstrable by much available evidence from various sources, being accepted as a cause, what is its relationship with the physical symptomatology of the disease?

Petersen[13] states in his text-book: "The physical disorders of dementia præcox have no pathognomonic value, though many have been studied and described. Among them are attacks of syncope, epileptiform, apoplectiform and hysterical seizures, localized spasms, tetany, transitory paralyses, aphonia, singultus, choreiform movements, athetoid ataxia, aphasia, exaggerated reflexes and increased mechanical irritability of the muscles, dilated pupils usually; vasomotor disorders (cyanosis, œdema dermographia, hyperidrosis); increased salivary secretion; pulse slow or rapid, often weak and irregular; subnormal temperature, amenorrhœa, diffuse enlargement of the thyroid gland; anæmia; emaciation in acute and subacute conditions, but rapid increase in weight in the later stages." To these I shall add a few other familiar symptoms to emphasize special points.

It must be granted that an interpretation of a morbid process capable of explaining all the physical signs of that process, must be fundamentally sound. This attribute the explanation submitted seems to me to possess, as we shall see presently, after outlining what to me is the secret of the disease.

Given a pathogenic toxic that is absorbed into the blood, it evokes, from my viewpoint, a defensive reaction in various ductless glands, the thyroid and adrenals in particular. Sometimes the thyroid is sufficiently enlarged to be noticeable before exhaustion atrophy has occurred in the organ. The adrenals have been found enlarged post-mortem by Parhon and Zugravu[14] and

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[13] Petersen: Church and Petersen "Nervous and Mental Dis," 6th ed., p. [illegible], 1908.

[14] Parhon and Zugravu: Arch. de Neurol., Nov., 1912.

Dercum and Ellis.[15] The excessive activity of the thyroid having for its purpose however, the destruction of poisons, its activity is such as to break them down, *i.e.*, to catabolize them, this process being in keeping with its familiar action as an anti-fat. Herein lies, it seems to me, the main fundamental feature of the morbid process of dementia præcox. Briefly, the patient is the victim of his defensive resources: *he undergoes psychical deterioration as a result of the active denutrition of his cortical cells (among others) through inordinate catabolism of the cellular fats of all neurons, lecithins and other phosphatids, cholesterol, etc., owing mainly to the excessive catabolic activity of his thyroid gland. This occurs especially during adolescence because his thymus, owing to the coincidence of puberty, is rapidly reducing the supply of nucleoproteins required by his cerebrospinal and peripheral nervous systems to build up these fatty bodies.*

We shall now see that this elucidates the physical symptoms of the disease, the mental symptoms being obviously due to progressive destruction of the cellular elements.

The vascular symptoms, "cyanosis, œdema, dermographia, hyperidrosis" with the "pulse slow or rapid often weak and irregular," "subnormal temperature and syncope," obviously denote the opposite of active metabolism. They point clearly to relaxation of the peripheral vessels known to attend *excessive* thyroid activity. The blood-pressure is generally well below normal, as shown by Lugiato and Channessian[16] and others, but variable in the same individual. The same irregular hypotony attends the cardiac muscle; hence, the frequent changes in the pulse-rate and vigor, either from day to day or within, in fact, a few hours. The circulatory torpor is sometimes rendered evident by reddening of the extremities, hands, feet, nose and ears. As an Italian alienist, Lugiato[17] states: "The patient is apt to present a rather delusive appearance of robustness, but in fact, he is feeble and torpid and even before the well-marked onset of the disease his circulatory system is apt to be poorly developed, his left ventricle small, his pulse feeble and of low tension, and his superficial veins not very distinct." It is to this vascular torpor that cyanosis—sometimes leading to gangrene—is due, the dermographia indicating capillary passive hyperæmia due to relaxation of the arterioles. It accounts also for the œdema, sometimes limited to circumscribed areas resembling fat pads or so infiltrating the whole body as rapidly sometimes to cause a "rapid increase in weight," and also the brain to such a degree as to have suggested the term "wet brain."

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[15] Dercum and Ellis: Jour. of Mental and Nerv. Dis., Feb., 1912.

[16] Lugiato and Channessian: Rev. sperm. di Freniatria, vol. xxxii, fasc, 1-2, 1906.

[17] Lugiato: Morgagni, Jan., 1907.

The eye fundus, examined in 109 cases by H. H. Tyson and L. Pierce Clarke[18] shows corresponding signs. "The primary changes," write these authors, "were in the veins which become dilated and tortuous and œdema follows, the changes being analogous to those seen in the passive congestion of the face and hands." What "anæmia" there exists is fictitious, for the red corpuscles count usually exceeds normal and is really due to the general hydremia.

The "hyperidrosis" is another symptom of vascular relaxation in these patients, the sweat-glands, owing to the torpor of their vascular supply, losing their tone and allowing the sweat to ooze out as it often does when death is near. A striking symptom, particularly noticeable in cases due to fecal stasis, is that the sweat itself gives off an odor—so repulsive in three of my cases as to make close proximity to them quite unpleasant. Others have compared it to the odor of small-pox cases. The "increased salivary secretion" is also due to relaxation of the glandular vascular supply.

"Syncope," the last of the vascular series, becomes a normal result of such a state of things. The low blood-pressure, the feeble heart action, the circular torpor—all of which tend to favor accumulation of the systemic blood into the splanchnic area—readily explains the cerebral ischæmia to which syncope is usually ascribed.

As regards the muscular system, proper, there is one perplexing symptom which nothing so far has explained. It is the automatism or wax-like position retained by the extremities, etc., when they are placed in that position. Precisely as would a jointed manikin, it is retained, no matter how uncomfortable or grotesque, until the limb or head is replaced. If, however, we realize that the functions of the central neurons controlling these movements are also inhibited through the paucity of fatty bodies in them, this "stereotypy of movement" as it is called, and which also involves the speech muscles, its cause becomes self-evident. The mutism is probably due to the same condition.

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[18] Tyson and Clarke: Jour. Amer. Med. Assoc., May 2, 1908.

The cellular denutrition also accounts for the "general emaciation" witnessed, and for the sexual anomalies. Indeed, as Plummer,[19] of the Mayo Clinic, states, "the thyroid hormone is fundamentally a part of the catabolic process of higher animal life." But how explain the epileptic attacks so common in these cases? As Pierce Clark[20] states, after a study of 150,000 seizures in ordinary epilepsy, "we must see the principle of pathogenesis in an initial toxin or auto-intoxication." Not only does this correspond with the cause of dementia præcox in point, but two of my own cases of epilepsy in children, one virtually an instance of status epilepticus, having from twenty to thirty fits a night, and the other three to five a night, treated on lines calculated to arrest toxæmia of intestinal origin, recovered perfectly, one being now of seventeen years' standing, the other of over four years. In this disease, as well as dementia præcox, the fit is the reflex expression in most cases, of a protective wave to overcome a tide of toxics which inadequate defensive endocrinic resources cannot destroy as fast as formed. Hence the improvement noted after such a paroxysm; hence also its recurrence as soon as another toxic wave has attained a certain level. The early "hysterical seizures; localized spasms and tetany," the "singultus," the "exaggerated reflexes" and "increased mechanical irritability" are but variants of the toxic process during the anabolic, *i.e.*, pre-catabolic stage, dependent upon the cerebrospinal centers irritated, the form of nervous instability peculiar to the patient and the efficiency of his defensive resources. It is perhaps unnecessary to state that not all the symptoms enumerated are observed in a given case; as Petersen says, they are not pathognomonic.

When "apoplectiform seizures" appear there is reason to think that a focal cellular autolysis has occurred, while in

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[19] Plummer: Trans. Assoc. Amer. Phys., July 25, 1918.
[20] Pierce Clark: Med. News, July 18, 1903.

"athetoid ataxia" and "aphasia" the "transitory paralyses" may all be results of the excessive catabolism entailing breaking down of the cellular fats of central neurons, as shown by chromatolysis of their cell-bodies. These explain not only the presence of these symptoms but also their prompt disappearance when the cellular autolysis ceases under appropriate treatment.

It is in the light of all these facts that we recall my previous statement that all nerve cells, including the cortical neurons (see Chapter X, this volume), are themselves vascular channels, and the seat of catabolism therefore, as are other cells —but in nerve cells breaking down their functional fats—we have a foundation for the fact, put in the words of Joseph Collins[31] that sufferers of the disease "lose their capacity for enthusiasm, are incapable of experiencing extremes of pleasure or pain, manifest a marked listlessness face to face with experiences of life that ordinarily provoke emotional display"; and finally "that aboulia, or loss of will power, is perhaps the most conspicuous hall-mark of dementia præcox."

The pathological findings of the cortical cell in dementia præcox are in keeping with the destructive process of excessive catabolism of cellular fats. As observed by various histologists, the chromatic substance of the cell bodies rich in fats, yields first; then the achromatic substance; the intracellular network which from my viewpoint contains the blood-plasma with its glandular hormones, while the nucleus and nucleolus which contain the dynamic bodies of the cell, its phosphorus-laden nucleins, gradually undergo atrophy and fragmentation.

An important point in this connection is the source of these nucleins, the feeders, at least in part, during the development of the child, of his nervous system, including the cortical cells now in question. We have seen that from my viewpoint, they are in part derived during the growth of the child from the thymus, and *that this gland begins to atrophy rapidly at the very time when dementia præcox usually occurs, i.e.,* during adolescence. Thus, as we have seen, while excessive catabolism uses up what nucleins the cortical cells, among others, contain, the supply of nucleins slowly declines.

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[31] Joseph Collins: Old Dominion Med. and Surg. Jour., Sept., 1908.

Indirect testimony to this effect is afforded by the fact that the therapeutic use of nucleinates has given good results, according to Donath and Lundvall, Bayard Holmes, and others; thymus gland extract has been given by Ludlum and Corson White[22] in six cases; "three gave excellent results," they state, "and are totally well at the present time."

Finally, another fact which has remained unaccounted for so far, and which the newer conception, submitted herein, explains, is the effect of partial thyroidectomy resorted to by H. J. Berkley, and Kanavel and Pollock; owing to some resemblance of the catatonic phase of the disease to exophthalmic goiter. R. Lewis,[23] who summarizes this work, states that it was followed by "a favorable and sometimes curative effect" in early cases, but with no beneficial result in advanced cases. It is obvious that this operation by partially removing the thyroid, reduced the destructive catabolism it induced. In early cases, when the cortical cells were not materially damaged, recovery could still take place, while in the advanced cases the disintegrated cortical cells were beyond any possible recovery. While this procedure is not warranted, now that some form of toxæmia within our reach is the initial cause, the fact remains that it emphasizes anew the importance of early curative measures as soon as a case of dementia præcox is clearly identified.

And this we have seen does not belong to the domain of the alienist. It belongs, if any result is to be attained in stemming the terrible and ever increasing sacrifice of young minds, to the general practitioner, who first sees the exposed child. Yet in order to permit of this, it is necessary to take into account the statement of Joseph Collins that "dementia præcox is a disease which the physician frequently encounters and often fails to recognize." This is in a great measure due to the complexity of psychiatric terminology, and it must be said also to the metaphysical trend of their interpretations, a field which the general practitioner usually fails to enter.

Reduced to its simplest expression, the *early symptomatology* of the average case of dementia præcox before the stage of insanity sets in is not difficult to recognize, though subject to many variations from the picture here given.

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[22] Ludlum and Corson-White: Amer. Jour. of Insanity, vol. lxxi, No. 4, April, 1915.

[23] R. Lewis: Jour. Amer. Med. Assoc., Oct. 1, 1910.

The patient, about the age of puberty, who may, perhaps, have done well at school, fails to sustain his general averages. He finds it increasingly difficult to concentrate his attention either upon his books or any work entrusted to him, and tends to drop his tasks unfinished. He may leave a position with no apparent excuse, disregarding promises and appointments, and on taking another, conducts himself in the same manner—a behavior differing totally from his former habits. He becomes listless, moody, constrained, taciturn and seclusive, showing an increasing tendency to ignore the external world. He also becomes careless in dress and appearance. His emotions seem also to have deteriorated; he no longer becomes enthusiastic over matters or events which formerly greatly pleased him. He shows no joy or sorrow and all tendency to emotional attachment—whether it include affection, altruism or love—steadily decline, until every finer attribute inspired by the love instinct seems to have disappeared.

His temper may also show a marked change, contrasting perhaps with what formerly was deemed a "good disposition." He tends to become surly; is easily angered and quick to quarrel. He is very positive in his likes and dislikes, obstinate and unreasonable in his demands and may show, if resisted, violent outbursts of temper, scream, weep and use violent and profane language. On the whole, he is very resentful of control—a defect which often entails the reformatory—and tends to oppose everything done for him. About this time an outbreak of some sort may occur; the sufferer, boy or girl, may run away and become exposed to the limitless dangers that the external world offers.

The excitement phenomena probably coincides with early irritation, direct or indirect, of the cortical cells by the pathogenic toxic, since they also occur in a measure, under the influence of alcohol and other stimulants or autolysis. Often from the very start the patient may complain of general malaise, a tendency to insomnia and headache.

Then appears what may be a second stage, probably coinciding with the effects of continued thyroid overactivity and catabolism of the cellular fats: catabolic dilatation of the systemic vessels and denutrition of the cortical cells, viz., that of psychic deterioration. The patient, while tiring easily and disinclined to do physical work, becomes increasingly apathetic, suspicious, particularly of the persons around him. His conversation, though showing but little impairment of memory, lacks intelligence, the sentences being at times disjointed, illogical. The power of reasoning seems in abeyance and he is no longer able to grasp even simple propositions. Hallucinations, illusions and delusions, sometimes of persecution, may then appear. Or, he may be loquacious, talking incessantly, often incoherently, and become noisy and destructive, or lapse perhaps into mutism, refusing to answer all questions.

Then follow the steady enfeeblement of all faculties, with all its distressing phenomena, many of which render the patient an object of repulsion to all who approach him. Steadily the cerebral cells have been destroyed until all hope of recovery is futile.

The number of complete recoveries in New York State Asylums, as given by H. M. Pollock[24] during 1916 was 21 in 21,070. This tells the story of what is to be expected when the case is allowed to go far enough to impose commitment to an asylum. And this is what the newer views concerning the source of dementia præcox and its treatment may enable us all to prevent, provided the family physician will familiarize himself with the earlier signs of the disease and institute active treatment before permanent cerebral lesions have had time to occur.

What some of these consist in we have already seen. The object is to seek and *remove any source of toxæmia which may awaken inordinate activity of the thyroid gland.* In some cases, in many perhaps, the source of the poison may be in the intestinal canal, and irrigation with saline solution of the toxic field through an appendicostomy or a cecostomy in the absence of the appendix, may be necessary. In milder cases, active purgation and a non-toxic diet may suffice. The stomach, particularly in gastroptosis, may also be the habitat of the pathogenic agent; frequent lavage here is indicated. In one of my cases, vaginal douches to check a foul greenish non-gonococcic leucorrhea, was immediately followed by marked improvement. A cystitis, particularly of the colon bacillus type, is another source of toxin. Briefly, all sources which experience has now pointed out as factors of hyperthyroidism besides the foregoing, such as tonsillar abscesses, adenoids, catarrhal disorders of the nose, nasopharynx and sinuses must be investigated and actively treated if need be.

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[24] H. M. Pollock: Dementia Præcox Studies.

The results of infectious diseases should be taken into account. It is quite possible that carriers of typhoid, diphtheria, scarlet fever, meningitis, and other pathogenic organisms, might be absorbing toxins from these organisms in sufficient quantities to sustain a toxæmia. Cultures of the secretions of children who present such histories will soon reveal the presence of such organisms.

Finally, the brain cells, as previously stated, obtain their nucleins, during the period of growth, mainly from the thymus. Some cases show the stigmata of thymic deficiency in the bones, teeth, etc., a fact observed by others. By means of thymus gland, nucleinates, or lecithins, we may not only benefit these special cases, but also those in which the stigmata do not exist, merely because, with the aid of judiciously selected food, these organic agents replace what excessive thyroid catabolism has served to destroy in the cortical cells.

Additional testimony is hardly necessary to show that dementia præcox belongs to the realm of the general practitioner. If he will but heed the plea, he may, through accumulated experience, develop the various lines of thought cursorily reviewed, and soon reduce materially perhaps the army of boys and girls, 15,000 strong, sequestrated each year in our asylums, there to remain till death releases them.

PATHOLOGICAL EFFECTS OF OVERACTIVE INTERNAL SECRETIONS.

The disease just considered, dementia præcox, but supplements Graves's disease or hyperthyroidia in demonstrating that an internal secretion, when from one cause or another it becomes unduly active, may initiate and perpetuate serious morbid processes. Many lives could be saved if this fact were duly recognized.

Diseases in which the predominating lesions are ascribed to the direct effects of bacteria on the tissues are numerous. The valvular vegetations of endocarditis and various spinal lesions followed by paralysis might be cited as examples. Are we sure that bacterial toxins and endotoxins as taught in text-books of practice are capable of injuring the tissues sufficiently to destroy them? The literature of the subject affords very little light on this question; various bacteria produce hemolysins, *i.e.*, substances which lake red corpuscles, and toxins which destroy leucocytes; but is this due to a direct dissolving power when toxin and cell unite, or is it due to the presence of other substances in the cell or the components of the cell itself? The supposed destructive action of bacteria, their toxins, etc., can more clearly be explained by a process in which certain internal secretions take part. The importance of such a pathogenesis lies in the fact that with a direct action of bacterial toxins on the tissues as viewpoint, our therapeutic resources are extremely limited, whereas if we can establish on a firm basis, a destructive process due to secretions whose action we can in a measure control, it will become possible for us to increase vastly our usefulness by arresting in time a frequent cause of death in many diseases and the destructive process which ends in the many forms of paralysis which now defeat our remedial efforts.

We have seen that three secretions play the main rôle in the autolytic process; 1, that of the thyroid and parathyroids which acts as opsonin to sensitize bacteria, their toxins, tissue wastes, fats, etc., to facilitate their catabolism or digestion in the phagocytes and blood; 2, that of the adrenals which endows the hæmoglobin with the power to become converted into oxyhæmoglobin and to sustain oxygenation and metabolism, and 3, the trypsic ferment of pancreatic origin which, under the influence of a rise in temperature due to increased oxygenation finds its digestive or proteolytic activity enhanced. Important in this connection is the now recognized fact that all cells contain such an enzyme, supplied to them through the intermediary of leucocytes, and also that both in the phagocytes and in the blood, it is this same digestive enzymes which break down bacteria and other harmful substances. Abderhalden has referred to them as "defensive ferments." When any of these pathogenic substances appear in the blood the production of "defensive ferments" is increased and that of the thyroparathyroid and adrenal hormones likewise—to constitute what I have termed autoantitoxin.

Under normal conditions of infection or intoxication a physiological increase of autoantitoxin occurs and the increased oxygenation and metabolism attending causes the phenomenon we term "fever" and which up to 104° F. or thereabout, may be said to act within safe limits as a defensive process. Yet we know that the familiar term *hyperthermia* betokens danger and that death threatens in a large proportion of cases. What happens under these conditions? From my viewpoint we are dealing with an infection or toxemia sufficiently severe to provoke a correspondingly active defensive reaction, the high temperature denoting the need of activating the digestive activity of the defensive ferment to its uttermost possibilities. Violence thus meets violence in the fray for supremacy. In the present connection, however, it should be borne in mind that the blood and tissue cells not only serve as battle field but also that they contain the trypsic enzyme. In view of this, the *tissue and blood cells* are themselves treated as if they were bacteria, they *are digested, broken down or hydrolyzed* by the ferment. This constitutes from my viewpoint what has been termed *autolysis* with destruction of the blood-cells, *hemolysis,* as initial step.

As to the nature of the autolytic process itself, I may recall that the thyroparathyroid secretion, acting as opsonin, sensitizes and softens the tissues as it does the germ or other substances it is to attack. The adrenal secretion, by oxidizing catalytically the nuclein of the tissue cells, raises their temperature. It is here that the autoantitoxin ferments acquire their hemolytic and autolytic power, as a result of this excessive temperature. Sensitized and softened by the thyroid hormone and the ferment they contain raised to its highest digestive efficiency the cells are partly or wholly destroyed.

We reviewed in the first chapter a number of disorders in which this morbid process prevailed. These will now be amplified and other disorders in which it prevails briefly described.

HEART.—The *valvular lesions* of endocarditis are now attributed to the direct action of pathogenic micro-organisms, but the irritant through which the germ is supposed to produce the histological changes witnessed has never been identified. The problem becomes still more obscure when the variety of diseases which can awaken endocarditis is taken into account, tonsillitis, scarlet fever, small-pox, pneumonia, tuberculosis, gonorrhea, meningitis, severe chorea, suppurative processes, etc., thus implicating the staphylococcus pyogenes aureus, the diplococcus pneumoniæ, the streptococcus pyogenes, the gonococcus and many other organisms—all supposedly doing their evil work merely through contact, aided perhaps by the friction of the blood stream. But the weakness of this explanation is self evident, and it will remain so until a factor common to all these diseases and pathogenic germs is found.

We have this factor, as previously shown, in the defensive ferments. The lesions coincide not with any special bacillus, but with those morbid processes in which the fever is high. The blood containing the ferments is especially active when it returns from the lungs to be thrust into the circulation by the left ventricle. It happens also that it is precisely the left heart which suffers most, while the vegetations are situated on that surface of the valves which is in contact with the blood. Briefly, we are not dealing at all with a direct action of micro-organisms, but with an autolysis or digestive process in which the autoantitoxin ferments attack the valves, the chordæ tendinæ and other exposed tissues which are the seat of vegetations.

Acute myocarditis is suggestively caused by the same class of diseases: Those infections mainly in which a high febrile process occurs: scarlet fever, variola, pneumonia, articular rheumatism including its causative tonsillitis, meningitis, gonorrhea, sepsis, etc., with the same multiplicity of bacteria as causative agents. As shown by Freund, precisely as is the case with endocarditis, circumscribed myocarditis is commonly a result of articular rheumatism. As in endocarditis, robust young adults of the male sex show a predilection for the disease as compared with females and weaklings. Here practically no attempt is made to explain the production of the lesions. De Vecchi found that the sterile blood of rheumatic patients gave rise to characteristic lesions in animals. As shown by W. H. Porter, moreover, the changes are not inflammatory, but various phases of a degenerative process, the degree of parenchymatous changes varying greatly in different cases. We are not dealing here with tissues traversed by a great mass of blood as is that which the left ventricle projects over the mitral valves, but with arterial blood also fresh from the lungs, rich in auto-antitoxin ferments—quite as capable, therefore, to produce autolysis of the myocardium and the whole gamut of degenerative changes resulting therefrom.

LUNGS.—*Pleurisy* is another disease attributed, in all its various forms, plastic, serofibrinous, purulent, etc., to the direct action of various pathogenic organisms. Here again we meet, besides the germs most frequently associated with the disease owing to proximity, the tubercle bacillus and the pneumonia diplococcus, pathogenic organisms encountered in inflammatory heart disorders, viz., the streptococcus pyogenes, the gonococcus, the typhoid bacillus, etc., all of which may awaken a sharp febrile reaction. Tuberculosis, gout and acute articular rheumatism, and pneumonia are its most frequent causative disorders, as they are of pericarditis which not infrequently occurs simultaneously—by extension through the lymphatics it is believed. In this disease several conditions may act as causal factors in which bacteria play a very secondary or no rôle. Pleurisy may develop, for instance, as a complication of Bright's disease, a condition in which accumulated excrementitious products which awaken a violent antitoxic reaction, must be incriminated. Chronic alcoholism is another condition in which a powerful defensive reaction accompanied by active oxidation of the alcohol, occurs for a time. Cancer must be regarded as an example of a disease capable of awakening sometimes, with extreme suddenness, an acute pleurisy, the widespread lesions of which present all the characteristics of an autolysis, the serofibrinous exudate being in reality the first step of the reparative process, just as it is in a burn of the second degree—all due to an excessive local defensive reaction with the defensive ferments as pathogenic agents.

LIVER.—We have just seen that chronic alcoholism predisposes to pleurisy. It is generally held, however, that alcoholism, by weakening the body, impairs its defensive resources and thereby favors the pullulation of bacteria and the development of disease. Still, as already stated, even where, as in the endocardium, the bacteria may be clearly discerned at the site of the lesions, there is no ground for the belief that they act directly upon the tissues. This does not mean, however, that they may not be the *indirect* causes; indeed, besides the fact that the blood contains an excess of defensive ferments, the presence of the bacteria over or in a given tissue provokes an accumulation of the protective substance to destroy the germs, precisely as occurs at the site of an injury. The aggregate of ferments thus formed being inordinately active, the bacteria are not alone attacked, but the tissues over which or in which they occur, likewise.

Atrophic or *alcoholic cirrhosis,* the most common form, is also produced, from my viewpoint, by a process such as that just described. As is well known, the fibrosis begins about the terminals of the portal vein where the alcohol, but slightly altered, first penetrates from the alimentary canal. Here it is actively oxidized, a process which occurs without injury if the quantity ingested is not excessive. But when, as in alcoholics, alcohol in quantities is absorbed, the often repeated local oxidation brings on local irritation, in turn followed by a defensive reaction which causes a local accumulation of defensive ferments proceeding from the portal terminals to the parenchyma of the hepatic cells. These along with the vascular tissues, undergo the characteristic degenerative changes, fatty in some and fibrous in others, more or less irregular at first, but finally invading the whole organ. Highly spiced foods consumed in large quantities, as in India, awaken the disease in the same way. Various poisonous materials, bacteria of various kinds, may also produce it. The pancreas which, as we will see, is essentially an organ in which autolysis is very active, is also involved in the morbid process, being likewise the seat of cirrhosis, as observed by Klippel and Lefas, D'Amato, Lando and others.

Acute yellow atrophy or *malignant jaundice* is the result of a rapid destruction of the liver cells, probably of an infectious nature, the causative organism of which has not as yet been discerned. There is an actual necrosis; the blood elements and the free pigment denote a rapid hemolysis, with crystals of bilirubin, cholesterin plates, fat droplets and granular débris strewn throughout the necrosed tissues. The picture at a certain stage reminds one of the effects of a cyclone. The blood at large shows hemolysis, while the heart, kidneys and other organs are the seat of fatty degeneration. Here we can hardly ascribe the destructive process to the chemical products, toxins or endotoxins of the hypothetical pathogenic organism, or to those of typhoid fever, syphilis, septicemia, puerperal fever, etc., which occasionally provoke it, for it may also occur as a result of phosphorus poisoning, chloroform anæsthesia, alcoholism, and other non-bacillary factors. In the light of the rôle ascribed to the defensive ferment in the other diseases reviewed, we are brought again to consider the likelihood of a destructive process due to an excessive local reaction of a defensive kind, an autolysis in the true sense of the word—a melting of tissue by its own juices, as it were, with ferments as active agents.

PANCREAS.—A trite example of the melting process by the ferments is *acute pancreatitis.* When due to specific fevers, pyemia, septicemia and other conditions attended by a sharp febrile reaction, this disease is as fatal as its pathogenesis is obscure. The pancreatic lesions as Opie and Meakins have held, are primarily necrotic. Here again, bacteria are found in great numbers precisely where the areas of coagulation necrosis occur. As in the liver in acute yellow atrophy, there is a mass of detritus containing blood corpuscles, and often vast hæmorrhagic foci and pus if the suppurative stage has been reached. Disseminated fat necrosis and areas of a substance resembling tallow or wax are found which recall similar conditions in other organs. This disease has been ascribed by Coenen to autolysis by the pancreatic secretion activated by bacteria; this is very nearly the process to which I would ascribe the lesions. Eliminating again the supposititious bacterial poisons we can today assert that both the adrenal and thyroid secretions occur in the blood-stream and that the pancreas receives its share. With its own secretions, particularly trypsin, the organ supplies the remaining and most active member of the digestive triad. Chiari has observed that the pancreas was often the seat of postmortem digestion—a mere continuation from my viewpoint of what had occurred during life.

INTESTINE.—In *typhoid fever* the lesions that occur in Peyer's patches or lymph glands, etc., of the intestines, are also ascribed to a direct action of the Eberth bacillus typhosus. Here, owing to the superficial location of the morbid process, its details, from the incipiency of the defensive reaction in the follicles to their destruction, may be accurately followed. Intense hyperemia, a great outpouring of lymph rich in phagocytes, accompanied by an equally great infiltration of the adjacent mucosa and muscularis first appear. Then occurs, in most cases, the formation of areas of necrosis beginning in minute points, attributed to vascular obstruction as well as to the bacillus—a process which finally gives rise to what has been termed "anæmic necrosis," but which to me is the first indication of the digestive action of the intestinal autoantitoxin ferments. As the necrotic process proceeds from the surface of the patch inward, sloughs are detached and cast off, and the *typhoid ulcer* is formed. Then may occur the complications of the ulcerative process—hæmorrhages due to erosion of perforation, peritonitis, etc., unless resolution precedes them. Relapse is clearly due to recurrence of the process in areas which the first process, owing probably to a local paucity of pathogenic bacteria, had failed to affect seriously. Many autopsies have clearly established this fact. Briefly, the landmarks of a digestive process by the autoantitoxin ferments seem to me clearly defined in typhoid fever.

NERVOUS SYSTEM.—Were I to enumerate all the nervous disorders in which autolysis due to autoantitoxin ferments may prevail from my viewpoint, practically the entire series of those in which paralysis occurs as a result of infection or intoxication would have to be included. To understand how such a process could occur at all, however, involves the acceptance of views which I advanced in 1903 (see page 518, this volume), and which are beginning also to gain ground, viz., that neurons are themselves circulatory organs in the sense that the adrenal oxidizing ferment, adrenoxidase, circulates in the axis cylinders, while the surrounding white substance of Schwann contains phosphorus-laden constituents which with the adrenoxidase liberate nervous energy. That the thyroid hormone and defensive ferments are represented in the nervous system as they are elsewhere in the body there can be no doubt, since a defensive reaction occurs when pathogenic bacteria penetrate it. What follows is not difficult to imagine.

The Treponema pallidum, for instance, stands out prominently as a cause of numerous neuroses, including tabes, as do other bacteria we have met elsewhere as causes of autolysis. In *acute myelitis* we have a reproduction of the morbid phenomena they cause; here syphilis, alcoholism, infectious fevers, pyogenic organisms, etc., may provoke softening and even cavities in the cord, fatty change, with quantities of cellular detritus and fibrosis to close the gaps with more or less sudden or general paralysis as result. *Tabes dorsalis* illustrates the slow type of spinal autolysis of the spinal roots invaded by the specific organism of syphilis or any other, and which the defensive autoantitoxin ferments concentrated there are trying to destroy. Gradually as the tissues yield to the morbid process, the train of symptoms appears, the preataxic stage denoting the irritative effects of the local defensive reaction and the ataxic stage that in which while destroying the causative bacteria, the autoantitoxin ferments have gradually destroyed the spinal tissues, fibrosis completing the obliteration of spinal functions and with paralysis as end result.

These few examples besides those submitted in the first chapter, must suffice to illustrate my meaning. They might be extended indefinitely almost, particularly in the nervous system, that great field, so faithfully studied, in which therapeutics has proved so sterile. Perhaps the most important suggestion this line of thought offers us is that remedial measures *have* failed because they were not timely. They suggest a new attitude in the treatment of all diseases due to infection or intoxication, that of seeking *measures calculated to anticipate lesions which a bacillus or a toxic can awaken by provoking too active a defensive reaction.* We must learn to check more efficiently an infection or an intoxication in its incipiency; we must learn, if they have reached beyond this stage, to prevent their morbid effects.

The first desideratum of course is to give more attention to the *early signs of disease;* true, many infections in their incipiency afford very little clue as to their true nature—sufficient at least to warrant any sort of specific medication. We must therefore resort to a measure which in practically any infection will suddenly awaken a defensive reaction sufficient to strike promptly the pathogenic organism or organisms that may be present. Our elders arrested infectious diseases far more frequently by means of their *calomel* powders than is done nowadays; they certainly did better than many of our modern graduates who give the pathogenic organisms full sway while the laboratory is being taxed for a diagnosis which often comes too late. Calomel is not only bactericidal in the entire alimentary tract, but from my viewpoint, it excites to sudden activity when given in small doses frequently repeated, all our autoprotective resources—sufficiently so in some instances to destroy the entire crop of pathogenic germs. *Vaccine therapy* has opened a vast field in this direction; doubtless that the *early* use of appropriate vaccines would save many lives.

In fully developed febrile cases, the particular complication to which the disease present may give rise, *endocarditis, acute rheumatism, acute pancreatitis* in *small-pox*, etc., should always be borne in mind as possibilities and due precautions taken when the temperature exceeds 104° F. materially. A feature of importance in the action of ferments is that their autolytic activity is raised up to certain limits by the surrounding temperature and that it is when hyperthermia begins that we must fear hemolysis, then tissue autolysis. The use of the ice-bag over the threatened organ, the heart, the pancreas, the liver, the spinal cord, etc., is doubtless beneficial, because it lowers the temperature, and thereby the aggressiveness of the ferment. Cool baths probably owe to this action their beneficial effects in typhoid fever. Hydrotherapy offers many resources in this connection. As to drugs, antipyretics are fictitious agents; they depress the surface temperature only in most instances, without affecting the deeper organs. Ample evidence is available in fact to show that they are positively harmful.

Probably the most active agent at our disposal in this connection is *saline solution.* By preventing any abnormal viscidity of the blood and facilitating osmosis, it favors the passage of toxin-laden plasma, toxic wastes, detritus, etc., into the lymphatics, and promotes elimination of their end products by the kidneys. The blood is thus relieved of at least a part of the pathogenic substance it contains. Using the expression of Sahli, we obtain lavage of the whole organism which is thus relieved of toxins. This reduces in proportion the volume of autoantitoxin ferments needed to defend the tissues exposed and we can surmise that cellular autolysis is thus more or less prevented.

We have as more tangible evidence, however, the clinical results observed and in earlier convalescence. Lenhartz, Häberlin, Todd and others have reported good results; Louis Lépine, J. Madison Taylor and others have ascertained their life-saving value in children; Lépine lays stress on the low mortality following the use of *sterile saline solution* in infectious diseases of infants. As I have urged before, it is not late, as a last resort, that it should be used, but *early,* so as to avoid any accumulation of toxins in the blood and its dire consequences. Nor is it necessary to flood the vascular system with it. In small children four ounces daily in two doses per rectum is all that is needed. Half *saline solution* and half *milk,* forming a pleasant drink, a glassful being taken four times daily, is quite enough for an adult. The subcutaneous use need seldom be resorted to if the oral or rectal method is begun early; but even here large quantities are not necessary.

FAILURE OF THE ADRENALS AS CAUSE OF DISEASE.

Addison's disease affords a clear example of death due to gradual failure of the adrenals through disease of these organs. We have also seen that various infections, overexertion, etc., may likewise exhaust these organs. In the present section two additional forms are described. In the one, influenza, interpreted from my viewpoint, is shown to be due to destruction by the specific bacillus, of the adrenal principle in the pulmonary alveoli; in the other, adrenal apoplexy, the adrenals themselves are shown to be the seat of local hæmorrhages which may cause death.

Influenza.—Although conservative estimates have placed the mortality of the 1918 pandemic at ten millions, Dr. A. J. McLaughlin, Assistant Surgeon General of the U. S. Public Health Service, wrote as recently as July, 1920,[28] in a comprehensive study of the subject: "It seems wise to review such facts and observations as we possess in the hope that an exposé of our *utter helplessness* may stimulate further research, and give us weapons with which to fight this scourge." The functions of the adrenals, interpreted from my viewpoint, seem not only to supply the key-note of the morbid process itself, but also to explain, what no other interpretation has so far done, the symptomatology and pathological findings of the disease and the manner in which the few drugs which have been found helpful cause their effects.

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[28] McLaughlin: Boston Med. and Surg. Jour., July 1, 1920.

Summarized, this newer interpretation is as follows: Infection through the respiratory passages is generally conceded; Blake and Cecil[26] having recently added conclusive testimony to this view. The process through which the influenza provokes the disease, however, has remained obscure, to such a degree in fact, that doubt concerning the validity of the Pfeiffer-bacillus as the specific pathogenic agent has been frequently expressed. Recent labors, however, notably those of Wohlbach,[27] Roos,[28] Duval and Harris,[29] have demonstrated its identity as such when sufficient care is taken, and suitable specimens and proper selective culture media are utilized in its cultivation. This fact, however, seems only to close the door to progress in view of the difficulties that the Pfeiffer bacillus had entailed ever since it has been isolated, in 1892. Yet it suggested that this bacillus might provoke the specific lesions in a manner still to be determined. A personal study in this direction then showed that when, despite the defenses, lymphoid and phagocytic, of the respiratory tract, the organism was able to reach the *pulmonary alveoli,* it found therein *all conditions required for its growth:* hæmoglobin, oxygen and temperature—precisely those found necessary in the laboratory. This accounted for the fact that, as observed by Winternitz[30] after ninety necropsies of influenza cases, "the most striking picture and one that is peculiar to this disease, is the *hyaline necrosis involving only the terminal bronchioles and alveolar walls,* sometimes involving only the epithelium but often involving all the structures of the walls." This localized primary lesion, which other pathologists have likewise recognized, Rickford[31] for instance, accounts for both the mild cases, an epithelial abrasion, and the more severe with their hæmorrhages, bronchiolar abscesses, and alveolar exudates, obliterating bronchiolites, etc., and favoring complicating pneumonia, broncho-pneumonia, etc., according to the multiplicity of other organisms present.

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[26] Blake and Cecil: Jour. Amer. Med. Assoc., Jan. 17, 1920.
[27] Wohlbach: Jour. of Immunology, July, 1919.
[28] Roos: *Ibid.*
[29] Duval and Harris: Jour. of Infectious Dis., Nov., 1919.
[30] Winternitz: Boston Med. and Surg. Jour., Feb. 20, 1920.

The participation of the adrenals appears when the symptomatology of the disease is analyzed in the light of the respiratory function I have attributed to these organs. It explains peculiar characteristics which no interpretation so far published has done. Interference with the alveolar functions explains the dyspnea and profound cyanosis of severe cases, but as many diseases interfere with respiration without causing such cyanosis, there must be some specific cause for it. This cause appears when it is recalled that hæmoglobin or blood can be dispensed with to obtain cultures of the B. influenzæ and, as shown by Contarn, spermatic fluid used instead. Now, this fluid has been shown by Poehl to contain the catalytic or oxidizing ferment also found in adrenin. In other words, it is the *adrenal active principle* itself which is taken up by the B. influenzæ which enables the hæmoglobin to become converted into oxyhæmoglobin. The whole sympathetic or chromaffin system including the adrenals, thus finds itself more or less depleted, leading often to a cyanosis so profound as to give the whole body a bluish-black or plum hue. As regards the adrenals proper, Baleno refers to a post-influenzal Addison's disease; Judson Daland[32] urges the close resemblance to the Addisonian syndrome, and found in all necropsies, thirty-seven "marked disease of the adrenals." He refers to an equal number of cases autopsied by Major O. L. Bothier at Camp Lee, who also found that "with the exception of the lungs no other internal organ suffered as much as did the adrenals."

Early relaxation of the peripheral arterioles, through loss of the adrenal principle, causes these vessels to permit flooding of the superficial capillaries with arterial blood thus causing the typical "cut sympathetic" carmine red congestion of the nasopharyngeal and oral cavities, and also the conjunctival congestion and other familiar signs of catarrhal congestion. This same arterial congestion occurring in the skin provokes a superficial rise of temperature, thus causing the pseudo-fever which fails to correspond with the pulse. In some cases, this relaxation involves the entire vascular tree, and the blood receding to the splanchnic area causing a condition opposite to that of fever; as observed by Samuel West, of St. Bartholomew's, such patients "complained of feeling so cold and chilly that nothing would warm them—not a roasting fire by day nor blankets galore and hot water bottles by night." Metabolism being inhibited by deficient oxygenation, the leucocytogenic tissues fail to create new cells and leucopenia occurs; a similar condition impairing the formation of protective antibodies, any predisposed area, intestinal, meningeal, aural, etc., becomes the prey of local specific bacteria, B. coli, meningococci, the streptococci, pneumococci, etc., that may be present. Hence the many local forms of the disease even though, as observed by Cerdeiras in seventy-nine autopsies, the pulmonary lesions, mild or severe, are invariably present, causing him to conclude that "influenza is preeminently a disease of the respiratory tract." The presence of methemoglobin also finds its normal explanation in the present connection, the persistent reduction of the unoxygenated hæmoglobin by the tissues. This applies likewise to the somnolence suggesting the "sleeping sickness" so-called, obviously due to the cyanosis which also affects the brain.

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[31] Rickford: Trans. Med. Soc. State of Penna.; Jour. Amer. Med. Assoc., Nov. 1, 1919.

[32] Daland: Med. Record, Jan. 31, 1920.

Among other riddles solved by this interpretation, is the familiar fact that young men between twenty and thirty years are the preferred victims. The defensive rôle of the respiratory passages being recalled, this phenomenon is explained when we take into account the greater respiratory activity of these young men, which causes the air contaminated with the Pfeiffer bacillus to reach the alveoli rapidly, *i.e.*, before sterilization of the air can have been completed. Again, we know that leaving the sick bed too soon is often followed by another and often more serious attack of the disease. With numerous alveoli the seat of active colonies, perfect quiet in bed, by insuring slow respiration, enables the expired air to be sterilized, while if the patient arises too soon, the increased respiratory activity prevents this protective process; the inspired current then carries active germs back to many previously unharmed alveoli—a true auto-infection.

That absolute rest has been found imperative is accounted for by the explanation of its mechanism. The value of the salicylates is also affirmed since by causing constriction of the arterioles, they restore the circulatory equilibrium. The best salt is the sodium salicylate which tends also to reduce acidosis. The use of adrenalin intramuscularly has been extolled by many French authorities. Strychnine in large doses is then indicated after a couple of weeks to stimulate the adrenals during convalescence, their insufficiency accounting for the familiar asthenia which follows the disease. If adrenalin has not been used suprarenal gland 2 grains should be given with each dose.

Adrenal Apoplexy.—A child—frequently an infant—previously well, or suffering perhaps from some infection, is suddenly seized with acute abdominal pain and vomiting, soon followed by a rise of temperature, collapse and death. Occasionally the fatal ending is somewhat delayed; hematemesis, diarrhœa and convulsions appear in rapid succession, soon followed by symptoms clearly traceable to the adrenals, to wit: sudden collapse, hypothermia, a very feeble and rapid pulse, shallow respiration, cyanosis, lividity and death. That we are dealing with a relatively common morbid process—seldom referred to in text-books—is shown by the fact that Mattée, Rolleston and Le Conte in an aggregate of 230 autopsies in the newborn found adrenal hæmorrhage in over 100 instances, or in 45 per cent. Hamill also considers adrenal hæmorrhage very common in the infant though the lesion is sometimes microscopic rather than macroscopic.

In adults, adrenal hæmorrhage is met with in 1 per cent. of all autopsies. When fatal in itself, the attack is also sudden, or preceded by a period of great lassitude, or, even, by a typhoid-like state with delirium and convulsions, with perhaps pigmentation varying from dirty yellow to light brown. Then follow in rapid succession very severe pain in the epigastrium and lumbar tenderness, incoercible vomiting, great weakness of the pulse, decline of the temperature and blood-pressure, cold sweats, coldness of the extremities and death in from a few hours to three days.

The established—that is to say, the generally recognized—features of this condition, are that a toxæmia or infection of some sort underlies it and that hæmorrhagic destruction of the adrenals is the cause of death. The direct cause of this in most cases, is the marked rise of blood-pressure which occurs *early* in infections, especially in septicæmia and erysipelas, tuberculosis, its most frequent cause in adults, on the one hand, and the great vascularity and friability of adrenal tissues on the other. In some instances the entire adrenal parenchyma is found destroyed, the medulla being converted into a pulpy mass.

Here again, we meet a condition in which a clear conception of the functions ascribed to the adrenals affords resources for a possible reduction of mortality. The aim here, and this applies to the entire field of febrile diseases, is to *prevent* adrenal hæmorrhage, for once the adrenals destroyed and the stage of collapse reached, there is little to be done. When *early* in the course of any febrile process, therefore, the fever reaches disquieting limits, and the *blood-pressure is high,* especially if there is epistaxis, hematemesis, or melena, or if there are petechiæ as in typhoid, spots of purpura, or of extravasations of blood as in various infectious diseases, or again, if the face becomes congested and swarthy as it does early in most cases of pneumonia, there looms up, among other dangers, that of adrenal hæmorrhage, through excessive centrifugal pressure within the delicate sinusoidal vessels of the medulla, with practically certain death as result.

How are we to avoid this calamity? Should we use antipyretics, the coal-tar products, for instance? Experience has shown that they are extremely pernicious—doubtless owing to their primary effect, which is to raise the blood-pressure. But experience has also shown that the physiologic saline solution, used intravenously in emergency cases, under the skin in threatening cases, and per rectum in all other cases, wards off the danger. If employed from the onset of the disease, even the approach of danger is prevented. This is especially marked in pneumonia, in which excessive blood-pressure entails also pulmonary engorgement—sufficiently intense, frequently, to cause death early in the course of the disease. Saline solution does not, as argued by some, increase the vascular tension even if injected intravenously; it increases at once the osmotic properties of the blood and as shown by the experiments of Sollmann, Briggs and others, any excess of fluid leaves the vessels at once. But, by diluting the blood, the adrenal principle it contains is reduced in proportion, and the dangerous general vasoconstriction induced by it is counteracted, thus relieving the adrenals of all disruptive pressure. The bactericidal and antitoxic properties of the blood are not reduced in the least by this procedure; there is ample evidence available to show, in fact, that they are enhanced.

CHAPTER VIII.

THE ADRENAL SECRETION AND FUNCTIONAL ACTIVITY.

In the first six editions I analyzed at length (1) the process through which the adrenal secretion (converted in the lungs into adrenoxidase, the oxidizing constituent of oxyhæmoglobin) carried on, from my viewpoint, its functions in various organs, and (2) the manner in which the nervous system governed its distribution. Briefly, I submitted the view that in the skeletal muscles and the lachrymal, salivary, sweat and mammary glands as examples of other organs, the adrenoxidase was the physico-chemical agent through which cellular metabolism was sustained by oxidation, and that there were two phases to this process: the *passive*, during which the organ was inactive owing to the reduced quantity of adrenoxidase supplied to the tissue-cells by the artificial blood; and the *active*, during which a more or less great increase of adrenoxidase reached these cells in a correspondingly greater volume of arterial blood, initiated and sustained functional activity in that same organ.

As to the manner in which the distribution of adrenoxidase was carried on, I submitted the evidence which had led to the conclusion that two kinds of nerves took part in the process: 1, motor or secreto-motor fibers supplied by one of the cranial nerves (the pneumogastric, facial, etc.), the terminals of which caused the arterioles to the organs to dilate and to admit an excess of the oxidizing substance of the blood, adrenoxidase, into their cellular elements, thus initiating active function, *e.g.*, contraction, secretion, etc.; 2, constrictor fibers, supplied by the sympathetic, which caused the previously dilated arterioles to contract, when this active function was to cease, thus diminishing the supply of adrenoxidase to the organ. This subject being considered at length in the second volume with explanatory illustrations, the reader is referred to that volume, pages 1115 and 1185.

The same method of nervous control was shown to prevail in the stomach—digestion being initiated by dilation of its arterioles through the pneumogastric and arrested by the sympathetic—and also in the intestines. These organs were shown, however, to initiate a defensive process against toxic proteins, bacteria and their toxins, etc., by means of their secretions and also through phagocytes supplied by the agminated follicles. The cæcum was included in this defensive mechanism, the vermiform appendix aiding it by supplying phagocytes and a secretion rich in bactericidal and antitoxic antibodies. This whole subject is also considered in the second volume (fourteenth chapter), to which the reader is referred.

The same functional features in respect to the liver and pancreas were analyzed in the first nine editions. It was then submitted as working postulates that:

1. The hepatic artery, owing to the oxidizing substance (adrenoxidase) that its plasma contains and the mode of distribution of its terminal capillaries, supplies the biochemic energy which initiates and sustains all reactions in the hepatic lobule that require oxygen.

2. The nervous supply of the liver is composed, first, of terminal subdivisions of the vagus, which enhance the activity of all its functions by causing dilation of the hepatic arterioles; and, second, of terminal subdivisions of the sympathetic, which, by causing constriction of these arterioles, reduce the functional activity of the organ.

3. In the normal subject the liver is anatomically isolated from structures that come into contact with bacteria, and protected against their intrusion by the bactericidal products of the intestinal glands and follicles.

4. The capillaries of the hepatic lobules, owing to the admixture therein of the hepatic artery's oxidizing substance (adrenoxidase) with the portal vein's waste-laden blood, are the seat of several functions now ascribed to the hepatic cell.

5. Blood-pigments and iron, derived from the intestine and spleen, simultaneously penetrate the hepatic lobule, and combine with the adrenoxidase therein to form hæmoglobin. The uncombined pigment is eliminated with the bile as bilirubin.

6. Urea is the end-product of three successive reactions, viz., (1) nitrogenous bodies are reduced to amides in the afferent veins,—mesenteric and portal; (2) the amides are dissociated into ammonia, carbonic acid, and water by the oxidizing substance (adrenoxidase) in the hepatic lobule; (3) urea is formed by synthesis in the efferent veins,—hepatic and vena cava.

7. The hepatic cell contains, besides its vacuoles and nuclei, numerous canaliculi (Schäfer) and a vesicular vacuole which opens into the bile-capillaries by a canaliculus (Kupffer); the canaliculi and the vesicular vacuole are probably connected.

8. Glycocholic acid and taurocholic acid are functional acids, inasmuch as they dissociate and appropriate waste-products, and, under the influence of the oxidizing substance, convert them into excrementitious products in the canaliculi of the hepatic cells.

9. The waste-products so converted by the biliary acids and the latter themselves, constituting bile, are transferred, along with other products for which the latter may serve as vehicle,—bilirubin, earthy salts, etc.,—to the vesicular vacuole of the cell and eliminated by the canaliculus that opens into the bile-capillaries.

10. The biliary acids, blood-pigments, iron, and other bodies or any of their components, that may prove useful to the organism are, entirely or in part, reabsorbed by the intestinal venules and returned to the portal circulation.

11. The sugars converted from intestinal foodstuffs in the intestines are brought to the hepatic lobule with the portal blood, and penetrate the canaliculi with the latter and with the oxidizing substance. During the bile-forming reaction the sugars are dehydrated, and, probably with the assistance of the cellular protoplasm, converted into glycogen.

12. The liver glycogen is converted into dextrose by an amylolytic ferment supplied by the pancreas as an internal secretion, which enters the portal circulation by the splenic vein.

13. Dextrose is distributed to the organs in which it is used as a source of energy by the blood, and only becomes vulnerable to oxidation when combined with products of metabolism furnished by those organs.

Another phase of the question requires analysis, however, one to which very little attention has been given in recent years, *i.e.*, the influence of the spleen upon pancreatic functions and the relations of this organ with the internal secretions. As will be shown sound experimental data tend to indicate that the spleen is concerned with the defensive functions in which we have seen the pancreatic internal secretion, or tryptic enzyme, takes part—all in addition to the hæmatopoietic credited to it.

THE INTERNAL SECRETIONS OF THE PANCREAS AND SPLEEN.

The pancreas and spleen are considered together because there is considerable evidence in favor of the view that they are functionally associated; and it is to give the analysis of this question and its relationship with the ferments furnished by the pancreas to the portal blood due prominence that we have, under other headings, considered the better-known functions of both organs.

To sustain our belief that liver glycogen is converted into dextrose by an amylolytic ferment supplied by the pancreas which penetrates the portal vein directly,—*i.e.*, by way of the splenic vein,—we were fortunate in having at our disposal the experiments of Croftan, which showed that suprarenal overactivity could so augment the functional activity of the ferment-producing organ as to induce a very great increase in the sugar eliminated. This feature requires further study, since it will tend to elucidate other functions of the pancreas.

We believe that we have conclusively shown that certain drugs and poisons increase the functional activity of the adrenals. The uniformity of the phenomena traceable to these glands under the influence of such agents seems to us to warrant the conclusion that, if we can demonstrate that glycosuria is also subject to the latter, its fluctuations following those of the suprarenal activity or insufficiency induced by them, a direct connection between glycosuria and suprarenal overactivity will have been shown. Yet we must bear in mind, in this connection, that all active drugs *may* have a primary action upon tissues for which they possess a specific affinity before the suprarenal protective functions are fully awakened. We have seen that even electrical stimulation of the splanchnic is only followed by vermicular motions of the intestinal wall after some time elapsed. But too much weight must not be given this feature, inasmuch as I have personally seen the typical symptoms of total suprarenal insufficiency occur in a dog within twenty seconds after a fatal dose of hydrocyanide of potassium had been administered. Large quantities of the less active drugs are more likely to reach the tissues for which they possess a special predilection, bromide of potassium, for instance, than such an agent as that previously mentioned. While, therefore, we cannot say that excessive formation of sugar, when drugs are given, is due only to overstimulation of the adrenals, we can say that all drugs can produce it when they stimulate suprarenal activity. Furthermore, it seems probable that some drugs not only do this, but they likewise, owing to their affinity for certain tissues, enhance the production of sugar by increasing the functional activity of the intimate structures of the organs concerned in its production from ingested substances—thus stimulating two different sets of organs simultaneously. Such an agent we probably have in phloridzin.

In an able and exhaustive review of the subject of toxic glycosuria, F. Cartier,[1] of Paris, says: "The symptomatology of phloridzin is very limited, seeing that it does not give rise to a true intoxication. . . . In man it is even possible to bring on glycosuria, and maintain it a long time, without giving rise to general disorders, provided a copious alimentation is insured." We have evidence in the last sentence that the main general result is an *excessive formation* of sugar, and, more carbohydrates being required, it is to an excessive production of the converting agent that we must ascribe this phenomenon. Still, if general symptoms are absent, what becomes of the suprarenal overactivity? Cartier answers this question when he says: "Yet *all* authors who have studied phloridzin unite in saying that the animal experimented upon becomes *voracious*, and, if not overfed, rapidly wastes. . . . When alimentation is insufficient, grave phenomena appear. Phloridzinic glycosuria has been obtained in animals entirely deprived of hydrocarbons; under these circumstances general symptoms *analogous to those of diabetic coma* have been observed."

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[1] F. Cartier: Thèse de Paris, 1891.

Osler[2] states that Frerichs recognized three groups of cases; two of these are of special interest to us: *(a)* Those in which after exertion the patients were suddenly attacked with weakness, syncope, somnolence, and gradually deepening unconsciousness, death occurring in a few hours. *(b)* Cases with preliminary gastric disturbance, such as nausea and vomiting, or some local affection, as pharyngitis, phlegmon, or a pulmonary complication. In such cases the attack begins with *headache,* delirium, great distress, and *dyspnœa,* affecting both inspiration and expiration: a condition called by Kussmaul *air-hunger. Cyanosis* may or may not be present. If it is, the *pulse* becomes *rapid and weak* and the patient gradually sinks into *coma,* the attack lasting from one to five days. The need of a copious supply of carbohydrates obviously points to increased oxidation. Indeed, complete absence of glycogen in the liver and muscles has been noted. The voracious appetite and rapid wasting further sustain this —and simultaneously, therefore, the presence of suprarenal overactivity. The italicized words in the list of terminal symptoms, on the other hand, as prominently point to the gradually deepening suprarenal exhaustion.

Alluding to the effects of acids in the production of glycosuria, Cartier refers to the experiments of Pavy[3] with phosphoric acid. An increase of sugar was noted in twenty minutes; fifteen minutes later a large quantity was present. In another strong, but *fasting,* dog the sugar was markedly reduced by a smaller dose. Hæmorrhagic infiltration of the gastric and intestinal tissues and hæmaturia were also noted. These are all familiar landmarks of suprarenal origin. Striking, in this connection, are the observations of Stadelmann,[4] who found that the production of CO_2 decreased in the rabbit during acid intoxications as it does in diabetic coma. In a foot-note Cartier says: "Voit and Pettenkofer and Gaethgens have peremptorily shown, by means of most precise experiments, that (1) the oxygen absorbed by a diabetic is much less than by a normal man, and that it decreases progressively until the end of the disease, when it is hardly equal to half of the normal quantity; (2) that the CO_2 exhaled is likewise reduced." That this is essentially due to suprarenal insufficiency—*i.e.*, reduced oxidation—is shown by the fact that, in a case of coma due to meningitis witnessed by Stadelmann, the proportion of CO_2 was 28.2 per cent.; while in diabetic coma the gradual decline is that observed in Minkowski's rabbits, which, from the normal 25 per cent., steadily dropped to 16, 8.8, then 2.9 per cent.

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[2] Osler: "Practice of Medicine," third edition.
[3] Pavy: Guy's Hospital Reports, vol. of 1861.
[4] Stadelmann: Deutsche med. Wochenschrift, Nov. 4, 1890.

We have seen that tetanus was partly due to adrenal overactivity. Cartier refers to the experiments of Claude Bernard, which showed that strychnine produced glycosuria in dogs. "It is unnecessary to reproduce here," says Cartier, "the symptoms of poisoning produced by this alkaloid; we will simply say that nothing recalls tetanus to such a high degree as does intoxication by it." We have another proof that it is due to an excessive production of a ferment or some other agency possessed of converting powers since Langendorff found that "glycosuria only occurs in frogs when the liver contains glycogen. . . . In the summer, when their liver contains none, strychnine does not cause diabetes in these animals."

We are reminded of the disorganization of hæmoglobin produced by advanced suprarenal insufficiency when, referring to curare glycosuria, Cartier says: "Others account for this glycosuria by an insufficiency of the respiration and by slowing of combustions. The dark coloration of curarized blood indicates this asphyxia." Even the nervous distribution, *as I interpret it,* including the basospinal connection between the pituitary body and the adrenals, finds itself sustained in a remarkable manner by the following lines of Cartier's in reference to morphine glycosuria: "An extremely interesting fact that all these investigations indicate is that one can produce with a toxic substance exactly similar phenomena to those recorded by Claude Bernard in his lessons at the College of France, and obtained by puncture of the medulla, and that these toxic glycosurias can in most cases be arrested, as are glycosurias of nervous origin, by severing the centrifugal nerve-impulse conductors. Indeed, section of the pneumogastric (centripetal nerve) does not prevent glycosuria caused either by Bernard's puncture or by morphine; but, on the contrary, *section of the splanchnic nerves* (centrifugal nerves) and of the medulla above the origin of these nerves prevents both the experimental diabetes of Claude Bernard and the toxic diabetes caused by morphine."

The list of drugs that are able to produce glycosuria could be indefinitely prolonged: it includes all those that produce suprarenal overactivity. But this does not mean that the ferment-producing organ is alone stimulated; glycosuria is but one of the manifestations of the exaggerated *general* metabolism induced, and oxidation processes are enhanced accordingly. Toxic glycosuria, therefore, only represents the surplus of sugar which oxidation processes have not consumed; the excess of sugar actually produced is probably far greater than the surplus which the urine shows. Again, certain drugs —phosphorus, for instance—do not produce glycosuria to any marked degree; as soon as the dose capable of causing it is reached, the adrenals lapse into insufficiency, and, if the dose is pushed to any extent, even the normal ratio is reduced. Antipyrin is now considerably employed in diabetes; we have seen that this drug and acetanilid readily produced suprarenal insufficiency and dissociation of the hæmoglobin molecule. This is sufficiently extensive sometimes to manifest itself as methæmoglobinuria or even hæmatoporphyrinuria. All these facts seem to me to indicate that *toxic glycosuria is primarily due to overstimulation of the adrenal system, the excessive functional activity which increased oxidation produces giving rise to an inordinate production of an agency that converts glycogen into sugar.* All these features will again be reviewed.

That the agency which converts glycogen into sugar is the amylolytic ferment produced by the pancreas to which I have referred is further sustained by the foregoing facts, especially in view of the amylolytic properties of the pancreatic secretion in the intestine. Since the conversion into sugar occurs during fasting as well as during digestion under the effects of toxics, the reaction can only include the hepatic glycogen and pancreatic ferment; and, there being nothing in the intestine to convert during fasting, the ferment must necessarily reach the glycogen by another channel. *May this not be the more direct route afforded by the splenic vein?*

Yet there is a possibility that the flow of amylopsin in the intestine, which the enhanced activity of the pancreas must undoubtedly increase, may be reabsorbed by the venules, and, being carried into the portal system, produce conversion of the glycogen precisely as if it had entered the portal vein by the way of the splenic vein. But we have seen that, while removal of the pancreas is rapidly followed by death, very large portions of the gland can be safely removed. Admitting that the operators may have left the portions related with the pancreatic duct, how could we account for the effects of transplanted fragments in arresting the glycosuria caused by removal of the pancreas, recorded by Minkowski[5] and Hédon?[6] As long as fragments transplanted subcutaneously remained normal no glycosuria occurred; it reappeared, however, when these fragments became histologically impaired. It is evident that the only channel here for the amylolytic ferment produced could be the blood. Thus carried to the heart, it then penetrated the liver by way of the hepatic artery, and reached the intercellular capillaries and the glycogen precisely as if it had penetrated the organ by way of the portal vein. Although but a small quantity of the ferment could thus reach the liver, it was evidently sufficient to convert the amount of glycogen required to build up the very limited proportion of sugar found in the normal blood, as previously shown. Again, we have seen that the product of intestinal reduction is maltose, while the urine of Croftan's animals when stimulated with suprarenal extract gave dextrose in very great quantities: a feature denoting successive processes. This and the other facts adduced appear to me to contribute additional evidence to my view that *the dextrose-forming ferment enters the portal system by way of the splenic vein.*

THE FUNCTIONAL RELATIONSHIP BETWEEN THE PANCREAS AND SPLEEN.

The internal secretion of the pancreas and that of the spleen may perhaps be best studied by submitting to a careful analysis the hypothesis advanced by Schiff, sustained by

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[5] Minkowski: Verhandl. d. XI Congr. für Inn. Medicin, Wiesbaden, 1892.
[6] Hédon: Archives de Physiologie norm. et path., vol. iv, 1900.

Herzen,[7] and defended by Lépine[8] and others that the spleen supplies a ferment which, when added to pancreatic juice, greatly increases its digestive energy. Schiff believed that the splenic substance played an important part in the genesis of the pancreatic proteolytic ferment, but Herzen attributed to it the function of converting trypsinogen into trypsin, the albumin-solving constituent of the pancreatic juice. This subject was more recently studied experimentally by Gachet and Pachon,[9] who were led to conclude, as previously suggested by Laguesse (1893) and Schäfer (1895), that the spleen furnishes a true internal secretion which possesses a special affinity for the pancreas, the protrypsin of which it transforms into trypsin, as suggested by Herzen. This substance loses its properties at the boiling-point; is precipitated, when in aqueous solution, by alcohol; and is, therefore, of the nature of a ferment.

Lépine also confirmed Schiff's and Herzen's view by experiments *in vitro* and by blood-analyses. He found that a mixture of pancreas and spleen-pulp in glycerin possessed far more active properties than pancreas alone similarly prepared. On the other hand, the blood of an animal deprived of its spleen proved almost inert as a tryptic, while the blood of a normal dog possessed distinct digestive powers. Analysis of the experiments of these various authors distinctly indicates that some function of the kind mentioned exists. The anatomical relations of the organs involved, however, make it impossible for the internal secretion referred to to penetrate the circulation without first passing through the liver *with the blood of the splenic vein, which collects the pancreatic internal secretion and carries it to the portal vein.* This fact seems to suggest that, besides the amylolytic ferment, the portal carries a ferment to the liver calculated to insure the tryptic action upon albumins and kindred bodies. If we consider that we have in the blood of the portal channels all the products of digestion and that trypsin is "applied solely to albuminoid conversions and changes" (Charles), the importance of the spleen's internal secretion will appear.

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[7] Herzen: Revue Générale des Sciences pures et appl., vol., 1895.
[8] Lépine: Société des Sciences Médicales de Lyon, July, 1895.
[9] Gachet and Pachon: Archives de Physiologie, April, 1898.

Albuminoids, especially those ingested with food, are not the inoffensive bodies that they appear to be; indeed, they constitute the foundation of some of the most dangerous substances that enter the organism when their molecular structure undergoes certain changes. Apart from any function of the spleen in the direction mentioned, the pancreatic trypsin supplied to the intestine—if we can judge by the manner in which a small remnant of pancreas will prevent glycosuria—must persist even when the pancreas is in a state of advanced disease. We saw that one-eleventh of the functional area of the adrenals sufficed to sustain the general oxidation processes. That the pancreas possesses at least four times more functional area than it absolutely needs has been experimentally demonstrated. With proper—fresh, uncontaminated—food, a normal organism is practically invulnerable, so splendidly is it armed against any chemico-physical decomposition that the ingesta may undergo. But these physiological defenses may be weakened through general or local adynamia, *i.e.*, lowered oxidation processes, and peptones, capable of yielding *toxalbumins, leucomaines, ptomaines,*—*all* albuminoids,—fail to undergo further splitting in the intestinal canal. Again, and under the same circumstances, notwithstanding the destructive action of the gastric and intestinal secretions, bacteria and their toxins may penetrate the debilitated villi and the portal circulation. The blood-stream, furthermore, may be invaded through peripheral organs not only by bacteria and their *toxins,* but also by *vegetable poisons* and venoms: *all* albuminoid substances, as previously emphasized. Even these do not represent all the sources of danger that a protective function, such as that represented by the pancreatic and splenic secretions, would have to meet, were they, as I believe, mainly intended to fulfill such a mission.

If toxic albuminoids reach the portal vein by way of the intestinal villi and the mesenteric veins, all conditions therein are most advantageous for the action which trypsin is known to exercise upon them: It acts with great energy in alkaline media, and the presence of oxygen does not inhibit its action;

if, therefore, the venous blood of the afferent channels should happen to contain an unusual amount of oxidizing substance through suprarenal overactivity, the tryptic disruption of peptones would not, to say the least, be prevented; in laboratory experiments the need of an antiseptic when pancreatic juice is used is well known; we have seen that, in the afferent vessels, the fluids derived from the intestines had been saturated therein with the antiseptic secretion of the glands of Brunner and Lieberkühn, and it is evident that their influence would normally continue in the venous channels; finally, the action of trypsin does not cease when the peptone stage is reached; it converts these into leucin, tyrosin, aspartic acid, etc., the fate of which derivatives I have traced down to urea, the end-product eliminated in the urine.

The rôle played by the spleen in the pancreatic digestion of proteids, and to which I add a prophylactic function, has been so ably reviewed by H. F. Bellamy in a comparatively recent number of the London *Lancet*[10] that I will utilize the greater part of his paper to illustrate the various features that appear to me to furnish a solid foundation, not only for the views of Schiff and Herzen, but also for my own.

The author reviews the history of the question as follows: "Corvisart found that in dogs in full digestion there was for a certain time a constant rise to maximum in the digestive power of the pancreatic juice, succeeded by an equally constant fall to minimum. The maximum was attained during the eighth hour after the ingestion of a meal; the minimum from the thirteenth to the eighteenth hours. Meissner announced that in fasting animals the pancreatic juice possessed little or no peptonizing power. Schiff, after a number of experiments on such animals as rats, guinea-pigs, rabbits, and young dogs or dogs of small breed, found that during fast the pancreas really possessed almost no peptonizing power; the albumin imprisoned in the duodenum remained there for whole hours without dissolving, the infusion of the gland giving results equally negative. On the other hand, in the case of ravens and adult dogs of large breed the pancreas preserved during fast a certain digestive power, even in animals in a condition of complete fast which had digested a copious meal the day before; under these circumstances, indeed, the infusion of the whole pancreas of a large dog was capable of digesting from 50 to 60 grammes of albumin. In such dogs this condition of weak digestion was maintained until toward the fourth hour after the meal, after which time digestion proceeded very much more rapidly, so that at the time of maximum the pancreatic infusion was capable of digesting from 50 to 60 grammes of albumin. As regard cats and small dogs, he was able to confirm the results of Corvisart. By these experiments, then, the above-mentioned observers succeeded in establishing the following two facts: (1) that the activity of the pancreatic juice or of an infusion of the gland is not continuous, but intermittent, and (2) that maximal activity appears regularly during the culmen of gastric digestion (from six to eight hours after a meal), at which time it is very considerable."

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[10] H. F. Bellamy: London Lancet, Oct. 27, 1900.

Passing now, for the moment, from the pancreas to the spleen, he proceeds briefly to examine the behavior of this organ in relation to digestive phases. "Lauret and Lassaigne in 1825 discovered that the spleen began to become congested at the moment when the stomach discharged chyle abundantly into the duodenum; that this is, however, merely a coincidence is shown by the fact that the congestion also occurs after ligature of the pylorus. Dobson in 1847 discovered that in a dog three hours after a meal the spleen is still as small and as anæmic as during fast; that it commences to dilate in the fourth hour after a meal; that five hours after it has attained its maximal turgescence, decreasing afterward from the seventh hour to attain toward the twelfth its minimal volume. Landois in the same year found that in the rabbit the relative weight of the spleen to the body-weight of the animal was the same two hours after a meal as after forty-eight hours of fast; that it increased considerably from the fifth hour, remaining high until the twelfth hour. . . . . . .

"The striking synchronism in the splenic congestion and the presence of trypsin in large quantity in the pancreatic juice or in an infusion of the gland was observed by Schiff and caused him to repeat all his former experiments on the tryptic digestion of albumins, this time on animals in which the spleen had been for some time removed and on others in which it was prevented from dilating by ligature of its hilum at the time of the experiment. He experimented in this way upon a very large number of dogs and cats; nearly all his experiments were double: *i.e.*, performed at the same time and in the same manner on two animals selected so as to resemble one another as much as possible, and in only one of which had the spleen been extirpated or ligatured. These experiments were of two kinds: (1) those conducted with pancreatic infusions, and (2) those carried out in the living duodenum, the following being typical examples:—

"*I. Infusions. Ligature of the Hilum of the Spleen.*—Two cats, after fasting for 19 hours, received as much meat as they would eat; 1 hour afterward they were etherized, and the spleens, which were found to be in a state of contraction, were brought out through a wound in the abdomen and their hila were encircled by strong thread; in one of the animals the hilum was firmly tied, but in the other it was simply encircled and a knot was tied, leaving the splenic circulation perfectly free (this was done in the endeavor to equalize traumatic conditions as much as possible). The spleens were then replaced in the abdominal cavity and the wound was sutured. On recovering from the anæsthesia the animals did not appear to suffer. They were killed 6 hours later. Gastric digestion was found to be more advanced in the animal in which the splenic vessels were tied; the pancreas of both was cut up into small fragments and infused with 100 cubic centimeters of water for an hour at 35° C.; the liquid was afterward decanted and returned to the warm chamber together with cubes of albumin.

"*Result.*—In 7 hours the pancreatic infusion of the cat in which the hilum was not ligatured digested 17 grammes of albumin; that of the other did not digest at all even at the end of 12 hours.

"This experiment was performed on a large number of cats and dogs and always gave the same result. In spite, however, of the perfection of gastric digestion in the operated animals, it was possible to lay at the door of traumatism the absence of duodenal digestion; to correct this the experiment was repeated as follows:—

"*Extirpation of the Spleen.*—Two dogs—one normal, the other having undergone splenectomy a month previously, but at the time of the experiment in perfect health—were operated upon, while fasting, as follows: Etherization, ligature of the pylorus, injection into the stomach, per œsophagus laid bare and opened, of 50 grammes of peptone and 2 grammes of dextrin; to allow drainage of swallowed saliva the œsophagus was ligatured below the opening. Both animals were killed five hours later, and each pancreas was infused for three-fourths of an hour in 100 cubic centimeters of water at 35° C. Although death had occurred before the most favorable moment for the experiment,—*i.e.*, in advance of the summit of the splenic curve,—the infusion coming from the dog with the spleen intact digested 17 grammes of albumin in 17 hours, while the other digested nothing even in 18 hours. Numerous experiments made in this manner always gave the same result. The spleenless dogs had in many cases undergone splenectomy several months before the experiment, and the determination in them of perfect conditions of health was always a matter of great care.

"*II. Experiments in the Living Duodenum. Ligature of the Duodenum at Both Ends.*—Two dogs after fasting for 17 hours received as much meat as they would eat and immediately afterward were operated upon as follows: Etherization, laparotomy, ligature of the pylorus and of the bile-duct, introduction into the duodenum of from 30 to 40 grammes of albumin, and ligature of the jejunal end. In one of the animals the splenic hilum was also ligatured. Both were killed 7 hours later.

"*Result.*—In the dog with the splenic hilum tied the albumin was found to be intact; it had, however, disappeared in the other.

"This experiment was also several times repeated on animals which had undergone splenectomy a long time previously, and always yielded the same result; it is, of course, capable of being combined with the preceding by making an infusion of the pancreas after the death of the animals. Such infusions give results in harmony with those furnished by the duodenum itself. Further, it will be remembered that in the pancreatic juice of dogs of large breed Schiff generally found, even while fasting, a certain quantity of trypsin; when the same were spleenless, however, he was unable to find any.

"*Digestion in the Normal Duodenum Provided with a Fistula.*—A duodenal fistula was established in a dog. After complete recovery a measured and constant quantity of albumin was introduced every day into the duodenum inclosed in a small envelope of fibrous membrane fixed to the cannula by a thread some centimeters long. The progress of digestion was then observed, the following results being obtained: 1. When the animal was fasting the albumin took from 5 to 6 hours to become dissolved. 2. When the albumin was introduced into the duodenum during the 2 to 3 hours immediately following the ingestion of a meal by the animal it remained unchanged. 3. When introduced 4 hours after a meal it disappeared very quickly,—in about half the time, in fact, occupied during fast. These facts having been duly noted, the spleen was then extirpated, and after complete recovery the same experiment was repeated; very different results were now obtained. Whether fasting or in full digestion the time taken for the digestion of the albumin was exactly the same, viz.: from 5 to 6 hours. The acceleration in the peptonization which had formerly appeared after the fourth hour of digestion, and which coincided both with the appearance of trypsin in the pancreatic juice and with the dilation of the spleen, was now absent. The slow digestion (from 5 to 6 hours) in this experiment was probably entirely due to the secretion of the duodenal glands, which possess only a very feeble digestive power; the active, rapid digestion was due to the appearance, in large quantity, of trypsin in the pancreatic juice: a phenomenon wanting in the spleenless animal. . . . Schiff endeavored to interpret the facts by the following theory: During the congestion of the spleen a substance is produced within it which, carried away by the blood, gives to the pancreas the wherewithal to form its peptonizing ferment. . . . In 1872, however, the theory of Schiff received a rude shock through the great discovery of the zymogens by Heidenhain and his pupils. From the researches of this observer it appeared that, as the gastric mucous membrane forms at the outset hardly any active pepsin, but a zymogen accumulating in its glands in the intervals of digestion, so the pancreas does not at once elaborate active trypsin but a substance destined to become trypsin under certain conditions and in a certain phase of the digestive act, this substance being, of course, the pancreatic zymogen trypsinogen, or protrypsin. The researches of Heidenhain are well known, and it suffices to recall here only one or more essential points: Thus from them we know that the pancreas of a fasting dog contains little or no trypsin, but merely trypsinogen; consequently its glycerin infusion possesses little or no digestive power; the infusion, however, of a dog in full digestion digests rapidly and copiously, because it contains trypsin. If the pancreas of a fasting dog be divided into two equal portions, one of which is infused at once and the other only after an exposure of 24 hours to the air, the first is found to be inactive, while the other is immediately and energetically active, from which it is clear that the inert trypsinogen which it contains becomes spontaneously transformed into active trypsin; indeed, it suffices to pass a current of oxygen through a pancreatic infusion, rich in trypsinogen and poor in trypsin (an active infusion), to transform it into an infusion possessing a digestive power. This transformation, then, is an oxidation, trypsin being oxidized trypsinogen.

"The fact observed by Heidenhain of the continuous formation and storing up of trypsinogen in the pancreas and its subsequent transformation into trypsin during the culmen of gastric digestion proved that the former substance at any rate enjoyed an origin quite independent of all influence outside the pancreas itself, and the hypothesis of Schiff as to the intervention of the spleen seemed, in consequence, to be at fault. But it was only the theory of Schiff which suffered by these new revelations; as far as the experimental results of the two observers were concerned, physiologists were face to face with two series of apparently contradictory facts—apparently because facts properly observed can never stand in contradiction with one another, and when they appear to do so it is merely because the interpretation of them is either false or incomplete. It fell to the lot of M. Herzen to unravel the tangled hypotheses. It appeared to him that, by modifying the hypothesis of Schiff as to the manner in which the spleen acts as a tryptogene, a fusion of the respective facts of Schiff and Heidenhain could be brought about, and that, far from being antagonistic, they could be shown to be reciprocally corroborative. He argued thus: since the zymogen, even in splenectomized animals, is being continuously elaborated, and therefore independently of the spleen and its periodical congestion, and that it accumulates in the gland-cells during fast, but that it becomes rapidly and copiously transformed into trypsin only in the presence of the spleen and in direct proportion to its dilation, it would seem feasible that the spleen produces, by 'internal secretion' during its congestion, an unknown substance, which, carried away by the circulating blood, transforms the inert zymogen already deposited in the pancreas into active trypsin destined to pass into the secretion of the gland, and that the influence exercised upon the zymogen by this product of the spleen seemed to be a condition *sine qua non* for the transformation of the former into trypsin, at least in the living pancreas, since in the dead organ or its infusion it is so transformed by direct oxidation. This hypothesis of Herzen would seem to be further confirmed by the fact gleaned from the researches of both Schiff and Heidenhain, to wit: that the holding in zymogen of the pancreas at a given moment either of fast or digestion is always in inverse ratio to its holding in trypsin, and *vice versa,* while the latter is always in direct proportion to the spleen dilation.

"So far so good. But Herzen reasoned further. If the spleen really produces, during its congestion, a substance which brings about the transformation of the pancreatic zymogen into trypsin, it would then be possible to seize upon this substance in the spleen itself while in its turgescent condition (from 6 to 7 hours after a meal), and by at once making an infusion of it and mixing a certain quantity of this splenic infusion with pancreatic infusion made from the pancreas of a fasting animal (very rich in zymogen and very poor in trypsin, and consequently nearly inactive) there could be obtained *in vitro* a rapid and copious formation of trypsin easily recognizable by the amount of proteid digested in a given time. The control experiment would also be very simple, consisting merely in mixing with the same pancreatic infusion that of a contracted and anæmic spleen, in order to observe whether it would have the same effect as that of the spleen dilated and engorged with blood. Artificial digestions actually carried out with these infusions gave enormous differences: whereas the pancreatic infusion alone, or that mixed with infusion of contracted spleen digested nothing or almost nothing, the same pancreatic infusion to which had been added infusion of engorged spleen digested rapidly and copiously; indeed, it had often completely digested its dose of proteid by the time that the other two, if digesting at all, had barely commenced. The mixed infusions thus behaved in the same way as a pancreatic infusion taken at the culmen of digestion.

"A large number of similar experiments were made with aqueous boric and glycerin infusions, each being double: *i.e.*, performed in two separate series of vessels, the one containing finely divided fibrin and the other equal-sized cubes of coagulated albumin. The results were always the same. . . .

"At the German Congress of Medicine held at Strasburg in 1886 Herzen exhibited several graduated flasks containing the residua of fibrin and albumin in a number of his digestions, the digesting liquid having been decanted and replaced by alcohol. The physiologists, who examined them all recognized that the difference between the residua left by the pancreatic infusions alone and those of the mixture of the pancreatic and splenic infusions were very obvious. In a private conversation with Herzen, however, Heidenhain made the following criticism: It is well known that the pancreatic zymogen is very greedy of oxygen; on the other hand, the spleen during its dilation is engorged with blood. The splenic infusions exhibited were intensely colored by dissolved hæmoglobin—*ergo*, the undoubted and considerable acceleration in digestion obtained by adding such a liquid to another containing trypsinogen could be quite simply explained by the rapid oxidation of the zymogen at the expense of the hæmoglobin. This objection disconcerted Herzen in no inconsiderable degree, and he lost no time in making it the subject of experimental inquiry. He at length succeeded in disproving it by the following excellent experiment: The pancreas of a normal fasting dog was infused in pure glycerin and the infusion was divided into eight equal portions. These eight portions were mixed with eight samples of blood received directly into a double volume of glycerin, of which four came from a fasting dog and four from a dog in full digestion with the spleen greatly dilated. The four samples were taken in both animals from (1) the femoral artery, (2) the femoral vein, (3) the splenic artery, and (4) a large splenic vein. The eight portions were then given the usual dose of fibrin and placed at a temperature of 40° C. Now, it is evident that the femoral and splenic arterial blood of the two animals contained more oxygen than their venous blood; the former, then, according to Heidenhain, should exercise a powerful influence on the digestion, equal in the two dogs. On the other hand, according to Herzen, the splenic venous blood alone should exercise this influence and especially that of the digesting animal. The result of the experiment was as follows: After one hour there was still no trace of digestion under the influence of the femoral blood, arterial or venous, nor of the splenic arterial blood of the fasting dog; first traces of digestion were beginning to manifest themselves under the influence of the splenic venous blood of this animal. Digestion was rather advanced in the case of the femoral arterial and venous blood and splenic arterial blood of the digesting dog; the fibrin had almost entirely disappeared under the influence of the splenic venous blood of the same animal.

"The answer could not be clearer: the product of the internal secretion of the spleen, borne therefrom by the circulating blood, is present during the period of the dilation of the spleen in feeble, but appreciable, quantity in the blood of the general circulation and abundantly in the splenic venous blood. The venous blood returning from the contracted spleen only contains it in very small quantities. This experiment, several times repeated, always gave the same result, showing that it is not the blood as such which favors the transformation of pancreatic zymogen into trypsin, but that, by picking up from the spleen the unknown substance possessing this property, the blood becomes its vehicle and means of communication with the pancreas.

"From the bulk of evidence collected by Herzen there thus seems to be very little room for doubt that, apart from hæmatopoietic, and possibly allied, functions possessed by the spleen, the organ furnishes a product of 'internal secretion' which causes in the pancreas the transformation of its inert zymogen into active trypsin."

Bellamy closes his article with a review of the criticisms to which the researches of Schiff and Herzen have been submitted. In the experiments of Lussana, in 1868, the spleens of three dogs were removed and the animals were subsequently killed to ascertain whether the extract of their pancreas would digest coagulated albumin. The pancreatic infusion of the glands of two of the dogs digested 0.25 gramme of albumin in 24 hours; that of the third digested 1.10 grammes in the same period of time. "The latter animal had, however, been killed three hours after a meal: *i.e.*, at a moment when, even had it been in possession of its spleen, that organ would not yet have commenced to become congested. The experiment, therefore, gave the result which might be expected,—viz.: no digestion,—for nobody would accept seriously the digestion of 1.10 grammes, knowing that the pancreas of a dog when digesting can dissolve from 50 to 60 grammes of albumin. . . ." Indeed, the experiments of Lussana appear to us to be confirmatory of Schiff's and Herzen's views.

Carvallo and Pachon also reported negatively, but, errors in their experimental procedures having been brought to their attention by Herzen, subsequent experiments caused Pachon and a new collaborator, Gachet, to reach the conclusions sustaining the views of Schiff and Herzen to which we have referred on page 368. "Nay, they did more," says Bellamy; "they invented an entirely new experiment, at once original and ingenious, which consisted in realizing *in vivo* what Herzen had hitherto only done *in vitro*. This experiment was as follows: A dog, which a long time previously had undergone splenectomy, was anæsthetized and half its pancreas was removed and immediately infused; at the same time a normal dog, in the height of digestion, was killed and its congested spleen was infused in water, and this infusion was injected into the venous system of the spleenless dog; from 15 to 20 minutes afterward the remaining half of the pancreas of the latter dog was infused exactly like the first; of the two infusions when given fibrin and albumin, the second only digested rapidly and copiously."

The investigations of Popelski are next reviewed. "In both normal and splenectomized cats," says Bellamy, "he collected the pancreatic juice by means of a cannula introduced into the duct of the gland, and was unable to find any difference in digestive activity. As, however, his cats had been fasting since the day before, his experiments were made outside the digestive period during which the spleen, becoming congested, furnishes abundantly its product of internal secretion which transforms rapidly and copiously the zymogen into trypsin." . . . "But Popelski also performed some analogous experiments on a dog with a permanent pancreatic fistula, made according to the method of Pawloff. The pancreatic juice of this animal was several times collected and examined before and after splenectomy without any difference in activity being demonstrable. This result, however, elicits no surprise in view of the fact that in both instances the juice was always collected immediately after a meal—*i.e.*,—again to repeat it—in advance of that digestive period during which the spleen enters into function and the pancreas abounds in trypsin; so that as well in this experiment as in that with his cats, Popelski was placed in that position in which the presence or absence of the spleen was a matter of perfect indifference. . . ." The discussion of the various features in point have led to considerable acrimony, but the impartial observer cannot fail to consider that the position of Herzen, of those reviewed, is the only tenable one.

In an article written since Bellamy's review was published Popelski[11] reiterates his views, and states that since it has been demonstrated that there exist in the organism *bodies in the nature of ferments possessing oxidizing properties,* which he believes to be derived mainly from leucocytes, the results obtained by Schiff, Herzen, Pachon and Gachet can all be explained by their action. During the height of digestion digestive leucocytosis prevails, and, an accompanying destruction of these cells yielding more oxidizing bodies, the latter, he thinks, are the source of conversion of protrypsin or trypsinogen into trypsin, which thus becomes a function of the blood. Thus, the spleen would have nothing to do with the process, the hyperæmia and dilation of this organ during the formation of trypsin being regarded merely as concomitant phenomena.

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[11] Popelski: Vratch, Feb. 3, 1901.

The only feature of interest to us in Popelski's last paper is the fact that his experiments were performed in accordance with the directions of Schiff. That he should be driven thereby to ascribe all the phenomena witnessed to the action of "oxidizing bodies" adds materially to the data contributed by Schmiedeberg, Jaquet, Abelous and Biarnés, and Salkowski, proving experimentally the existence of an oxidizing substance, and is suggestive. Indeed, when, in addition to this, we realize the strength of Heidenhain's position, the manner in which it shook to its very foundation the equally strong position of Schiff's views as developed by Herzen, by pointing to *the influence of oxygen* as another agency through which trypsin could be developed from trypsinogen, "trypsin being oxidized trypsinogen," the following query suggests itself: Are we not dealing with two processes working in sequence, a part of the trypsinogen secreted in the splenic vein being converted by the splenic secretion for use in the portal vein, and the rest being converted, when the arteries are reached, by the oxidizing substance?

To determine whether such a deduction is at all warranted or whether it is subject to modifications through which the various views submitted and our own can be conciliated, we find it necessary to closely analyze the manner in which the pancreas and the spleen are functionally governed.

THE FUNCTIONAL MECHANISM OF THE PANCREAS.—The pancreas will first receive our attention. Referring to this organ, Howell says: "Until recently little direct evidence had been obtained of the existence of secretory nerves. Stimulation of the medulla was known to increase the flow of pancreatic juice and to alter its composition as regards the organic constituents, but direct stimulation of the vagus and the sympathetic nerves gave only negative results. Lately, however, Pawlow and some of his students have been able to overcome the technical difficulties in the way, and have given what seems to be perfectly satisfactory proof of the existence of distinct secretory fibers comparable in their nature to those described for the salivary glands. The results that they have obtained may be briefly stated as follows: Stimulation of either the vagus nerve or the sympathetic causes, after a considerable latent period, a marked flow of pancreatic secretion. The failure of other experimenters to get this result was due apparently *to the sensitiveness of the gland to variations in its blood-supply.*[12] Either direct or reflex vasoconstriction of the pancreas prevents the action of the secretory nerves upon it. Thus, stimulation of the sympathetic gives usually no effect upon the secretion, because vasoconstrictor fibers are stimulated at the same time; but if the sympathetic nerve is cut five or six days previously, so as to give the vasoconstrictor fibers time to degenerate, stimulation will cause, after a long latent period, a distinct secretion of the pancreatic juice."

The quotation almost suffices to show that the sympathetic fibers are vasoconstrictors as elsewhere, in the light of our views, and that the secretory nerve is the vagus. This view is conclusively supported, however, by evidence from other directions. As to the vagus, François-Franck and Hallion[13] in addition to the dilator effects produced on the liver state that "this vasodilator action is also found in the pancreas." Stimulation of the peripheral ends of both vagi, after section, between the cardiac plexus and the diaphragm caused a wide dilation of the pancreatic vessels, which persisted some time, entailing a lowering of the aortic pressure. They also obtained dilation of these vessels reflexly, by stimulating the central end of the nerve after it had been cut on a level with the œsophagus. We have also in the experiments of Mette[14] and Kudrewetzky[15] evidence of the direct action of vagal stimuli upon muscular fiber. Having observed that the secretion caused by stimulating one vagus could often be arrested by exciting the other vagus, he concluded that this nerve contained antagonistic fibers. This dual set becomes unnecessary, however, if stricto-dilation is accepted as the mechanism of the vasodilation observed by François-Franck and Hallion. Indeed, vagal stimuli capable of causing contraction of the vascular *muscles* to which stricto-dilation is due, can as well induce contraction of the muscular coats of Wirsung's duct, and thus arrest the flow of secretion of pancreatic juice precisely as it does that of bile.

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[12] All italics are our own.

[13] François-Franck and Hallion: *Loc. cit.*

[14] Mette: Archiv f. Physiol., Suppl. Bd., 1894.

[15] Kudrewetzky: *Ibid.*

As the sympathetic supply François-Franck and Hallion[16] obtained plethysmographically vasoconstrictor effects on stimulating the splanchnic, and traced the constrictor fibers to the cord. The fibers were supplied through the fifth thoracic communicating branches to the second lumbar inclusive, the majority of them reaching the solar plexus by way of the greater splanchnic. The fibers then formed, they contend, "a secondary plexus enveloping the pancreatic artery." They also state that "this arterial path seems to be the only one, since the destruction of the fibers that accompany the artery suppress the pancreatic vasoconstrictor effects of any sympathetic branch stimulated." Again, Popelski[17] refers to various ways in which inhibition of the flow of secretion may be caused. Among these are: Stimulation of the vasoconstrictor fibers, and stimulation of "secretion-inhibiting" fibers supposed by him to represent a special set. The mode of termination of the sympathetic fibers on the pancreatic artery as given by François-Franck and Hallion readily accounts for the inhibition caused by excessive excitation of the nerves. These (sympathetic) fibers are thus evolved from the suppositious special "secretion-inhibiting" nerves—a rather incongruous combination, since by arresting the flow of blood to the organ, they prevent and may arrest the secretory process.

It is evident that these vasoconstrictor fibers are distinct from the true secretory fibers, for Pawlow[18] says, alluding to Popelski's work: "By a careful preparation of the nerves, some branches were discovered whose excitation caused a secretion without any latent period almost as promptly as the chorda expels saliva. From the latter fact we must conclude that in the branches mentioned, the secretory fibers of the pancreas have been anatomically separated from the inhibitory." Finally, a proof that we are dealing with exaggerated constriction ending in experimental inhibition and not with a true secretory nerve is afforded by the following observation of Kudrewetzki's[10]: "If the sympathetic nerve be excited by means of an induced current, a gentle intermittent advance of the secretion is observed, but only during the first few seconds; during the later stages of the excitation, and after its stoppage, the secretion is completely arrested." We have here, obviously, the identical result observed in the submaxillary gland when the cervical sympathetic is stimulated—a brief exacerbation of activity due to the propulsion of a small quantity of blood into the secretory elements—and simultaneously additional evidence that the sympathetic in the pancreas fulfills vasoconstrictor functions.

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[16] François-Franck and Hallion: Archives de physiol. norm. et pathol., T. ix, p. 661, 1897.

[17] Popelski: Centralbl. f. Physiol., Bd. x, S. 405, 1896.

[18] Pawlow: "The Work of the Digestive Glands," Eng. Trans., London, 1902.

This involves the conclusion that as elsewhere the blood-plasma—laden with oxidizing substance—is able to reach the glandular cells. This is shown by a brief review of the relationship between the nervous and vascular structures of the organ.

Referring to the blood-vessels, Piersol says: "The larger arterial branches run within the interlobular connective tissue, sending off vessels which pass between the lobules and supply the glandular parenchyma with twigs. These latter enter the lobules and form *net-works which inclose the individual acini within the capillary reticulum.* The capillaries lie beneath the basement membrane in close relation with the glandular epithelium. The veins accompany the arterial trunks within the connective tissue." A similar arrangement prevails in the distribution of the nerve-terminals. According to Ramón y Cajal and C. Sala, the pancreas contains many nerve-cells and fibers of Remak. Some cells are found in the interacinous spaces; others are in contact with the intrinsic vascular walls, and *their finer prolongations surround the glandular cells.*

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[10] Kudrewetzki: Quoted by Pawlow: *Loc. cit.*

Those connected with the vessels *form a plexus around them,* and send extremely fine filaments to the muscular elements. Alluding to the nerve-cells, Ramón y Cajal says: "We may consider this cell as a special cell, all the prolongations, or almost all the prolongations, of which possess the meaning of nervous prolongations *contrary to the cells of the sympathetic chain,* that have two kinds of prolongations: along one, or fiber of Remak, for the viscera, and short prolongations comparable to the protoplasmic prolongations of cerebro-spinal cells, destined to establish relations by contact between the neighboring cells of a ganglion." Berdal, who quotes the above, therefore recognizes two varieties of nerve-fiber in the pancreas: "1. The nerve-fibers formed by the cellular prolongations and which supply the periacinous and perivascular plexuses. 2. The nerve-fibers derived from the sympathetic nerves which penetrate into the pancreas *with the vessels.*

On the whole the functions of the pancreas appear to be governed as follows:—

1. The nervous supply of the pancreas is derived from the vagus and the sympathetic systems.

2. When the secretory functions of the organ are to be enhanced, the vagal terminals cause vasodilation of its arterioles, thus increasing the arterial blood circulating through it.

3. When the functional activity of the pancreas is to be diminished its arterioles are caused to contract by the sympathetic nerves, and the blood circulating through the organ is reduced.

FUNCTIONAL MECHANISM OF THE SPLEEN.—The innervation of the spleen includes, as a predominating feature, the distribution of a fair proportion of the terminal fibers to the muscular elements, which, in man, are mainly supplied to the trabeculæ. "We have evidence," says Professor Foster, "that the muscular activity of the spleen, whether of the muscular capsule and trabeculæ and arteries combined, or of the latter alone, is under the dominion of the nervous system. *A rapid contraction* of the spleen may be brought about in a direct manner by stimulation of the *splanchnic or vagus nerves,*" . . . "it may also be caused by stimulation of the *medulla oblongata* with a galvanic current or by means of *asphyxia.* Though the matter has not yet been fully worked out, we have already sufficiently clear indications that the flow of blood through the spleen is, through the agency of the nervous system, varied to meet changing needs. At one time a small quantity of blood is passing through or is being held by the organ and the metabolic changes which it undergoes in the transit are comparatively slight. At another time a larger quantity of blood enters the organ and is let loose, so to speak, into the splenic pulp, there to undergo more profound changes, and afterward to be ejected by rhythmic contractions of the muscular trabeculæ."

That rapid contraction of the spleen should occur under stimulation of the splanchnic nerve is easily accounted for when the rôle of sympathetic nerves—those it supplies the organ—is considered to be that I have attributed to them in the foregoing chapters: that of vasoconstrictor. Indeed, it is plain that under stimulation these nerves should reduce the caliber of the arterioles, and, therefore, the volume of blood admitted into the organ, and that it should contract rapidly owing to continued depletion of its veins. The constrictive effect of stimulation of the medulla on the arteries we have repeatedly seen; as this is due to contraction of their muscular coats, the spleen is evidently influenced in a manner similar to that following stimulation of the splanchnic, the smallest arteries being the first obstructed under violent vasoconstriction.

But why should stimulation of the vagus also induce splenic contraction? This requires an examination of the distribution of the nerve-terminals. The innervation of the spleen was studied by Kölliker in various animals,[20] and his observations, when viewed in the light of my conception of the functional mechanism of glandular organs, are suggestive. "The vasomotor nerves enter the organ with the large arteries. In the *walls* of the large arteries the main trunks form a well-marked superficial *plexus* with oblong meshes in the adventitia, and a *deep,* more quadrate *net-work* in the tunica media; some end in the little branched arborizations in this coat. The smaller arteries and the trabeculæ receive their nerves from the rich maze of fibers in the pulp, consisting of axis-cylinders, which, however, do not anastomose. Other fibers form a plexus on the surface of the trabeculæ, and from this fibrils penetrate *into* the interior of the trabeculæ *(which contain much smooth muscle)* and end by free arborizations." Free terminals, which Kölliker regards as sensory fibers, were also found. When we consider that the trabeculæ penetrate deeply into the interior of the organ from the inner surface of the capsule in every direction, thus forming a spongy frame-work, and that the muscular capsule overlying the organ and this spongy framework, is also supplied with vagal nerves, its contraction under the influence of the latter under stimulation also becomes self-evident in the light of our views: The vagus acting as a vasodilator allows an excess of blood to penetrate into the muscular elements, causing them to contract and thus to diminish the size of the organ. Indeed Roy[21] who first called attention to the rhythmic contractions of the spleen, ascribed them to impulses received by way of the vagus.

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[20] Kölliker: Sitzungsbericht d. Würsb. Phys. med. Gesellschaft, No. 2, [illegible].

A feature of the experimental work upon this organ which tends greatly to produce confusion in the interpretation of its function, is the belief that it is supplied with inhibitory fibers. Thus, according to Schäfer[22] these fibers are contained in the splanchnic nerves and their stimulation "produces a dilatation of the spleen." It is plain, in the light of our interpretation of "inhibition," that we are merely dealing with an experimental phenomenon due to the excessive vasoconstriction which electricity produces when applied to sympathetic vasoconstrictors, and that the organ does not receive "inhibitory fibers" as textbooks call them.

The interpretation of the splenic functional mechanism in accordance with our views is greatly facilitated when the microscopical anatomy of the organ is considered in the light of F. P. Mall's[23] researches. The organ is divided, as is the liver, into lobules, each of which is bounded by "interlobular" trabeculæ: those to which we have already referred. Each lobule is about 1 millimeter in diameter, is partitioned into about ten compartments by intralobular trabeculæ, and receives an artery which sends minute branches to each compartment. There is also considerable analogy between each one of these compartments and the hepatic lobule, the hepatic cells being represented by masses of pulp separated by venules, which vessels carry back to the veins leading to the greater splenic vein the various elements transferred to the liver. The pulp itself is made up of an extremely delicate reticulum, in which are found red corpuscles, lymphocytes, remains of corpuscles with or without pigment, etc. The arteries—which bring to the organ oxidizing substance—soon after entering the organ assume an unusual shape: their outer coat becomes lymphoid, forming nodules similar to the solitary follicles of the intestine,—*i.e.*, the Malpighian corpuscles,—in which lymphocytes are formed. When, after numerous subdivisions, their diameter becomes greatly reduced, the arteries resume their normal adventitia and on reaching the pulp in the compartments break up into minute capillaries. The arrangement is, after all, an uncomplicated one, and similar, in general plan, to that of other organs reviewed.

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[21] Roy: Journal of Physiol., vol. iii, p. 203, 1880-2.

[22] Schäfer: "Proceedings of Royal Society," London, 1896, vol. lix, No. 355; and Journal of Physiology, 1896, vol. xx.

[23] F. P. Mall: Johns Hopkins Hospital Bulletin, Sept., Oct., 1898.

The connection between the nervous supply of the spleen and that of the other digestive organs becomes evident when the distribution of the cœliac-plexus branches is recalled. "The splenic plexus," say Pick and Howden,[24] "is formed by branches from the cœliac plexus, the left semilunar ganglia, and from the right pneumogastric nerve. It accompanies the splenic artery and its branches to the substance of the spleen, giving off, in its course, filaments to the pancreas (pancreatic plexus) and the left gastro-epiploic plexus, which accompanies the gastro-epiploica sinistra artery along the convex border of the stomach." If we append to this Kölliker's description of the intrinsic nervous supply and the manner in which it is connected with the blood-vessels, it will become apparent that we have a counterpart of the vasculo-nervous mechanism of all the other organs of the digestive system we have studied, viz., a system of vagal fibers capable of inciting the spleen to increased functional activity by causing an excess of blood to enter the organ, and sympathetic fibers to reduce its functional activity by causing the vessels to resume their normal caliber.

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[24] Pick and Howden: "Gray's Anatomy," p. 808.

The functions of the Malpighian corpuscles around the vessels would thus be insured by fibers from the vagus. Indeed, Fusari[25] traced nervous filaments within these bodies. The pulp is also possessed of a "rich maze of fibers consisting of axis-cylinders"—doubtless sensory structures. But here an independent motor supply must also be present, since we also have fibers that form "a plexus on the surface of the trabeculæ," filaments from which penetrate *into* the trabeculæ. These, we have seen, contain much smooth muscle, and the nerve-filaments are connected with them by "swellings" (Fusari), evidently end-plates. Kupffer's bile-alveolus, with its canaliculi, is recalled by a similar receptable: *i.e.*, Mall's "intralobular venous spaces," which form the starting-point of the venules that ultimately end in the large trunks leading to the splenic vein.

On the whole, we may conclude as follows:—

1. The nerves of the spleen are derived from two autonomous sources, the vagus, or pneumogastric, and the sympathetic system.

2. The functional activity of the spleen is incited by the vagal nerves distributed to its arterioles: by causing dilation of these vessels, they admit an excess of blood into all the structures of the organ, causing the latter to dilate.

The vasoconstrictor functions of the sympathetic are as evident here as in other organs studied. "The spleen," says Howell, "is supplied richly with nerve-fibers which, when stimulated either directly or reflexly cause the organ to diminish in size. According to Schäfer these fibers are contained in the splanchnic nerves, which carry also inhibitory fibers whose stimulation produces a dilatation of the spleen." The sympathetic supply of the spleen has been clearly shown. Bulgak[25a] obtained vasoconstrictor effects, the organ becoming pale and shrunken, by stimulating fibers which he traced to the semilunar ganglion and thence to the left splanchnic. Tarchanoff reached similar results but by stimulating either splanchnic. Schäfer and Moore studied the same subject by means of a plethysmograph specially constructed to avoid any obstruction to the circulation in the organ's extrinsic vessels. They found the spleen extremely responsive to blood-pressure fluctuations, and obtained constriction by stimulating either splanchnic, the left, however, giving more marked results than the right. The constrictor fibers were found to raise from the third thoracic to the first lumbar inclusive, the most active arising from the sixth, seventh, and eighth thoracic. This evidence clearly shows that the rôle of the spleen's sympathetic supply is purely vasoconstrictor. Hence:—

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[25] Fusari: Archives Italiennes de Biologie, Turin, vol. xix, p. 288, 1894.

[25a] Bulgak: Virchow's Archiv. Bd. lxix, p. 181, 1877.

3. When the functional activity of the organ is to be diminished, the sympathetic fibers cause constriction of the arterioles, thus reducing the volume of blood admitted into the organ and passive contraction of its capsule.

The rôle of the spleen has not been so far clearly established. Howell, in the second edition of his text-book (1907) writes in this connection: "As to the theories of the splenic functions, the following may be mentioned: 1. The spleen has been supposed to give rise to new red corpuscles. This it undoubtedly does during fœtal life and shortly after birth, and in some animals throughout life, but there is no reliable evidence that the function is retained in adult life in man or in most of the mammals. 2. It has been supposed to be an organ for the destruction of red corpuscles. This view is founded chiefly on microscopical evidence according to which certain large amœboid cells in the spleen ingest and destroy the old red corpuscles, and partly upon the fact that the spleen tissue seems to be rich in an iron-containing compound. This theory cannot be considered at present as satisfactorily demonstrated. 3. It has been suggested that the spleen is concerned in the production of uric acid. This substance is found in the spleen, as stated above, and it was shown by Horbaczewsky that the spleen contains substances from which uric acid or xanthin may readily be formed by the action of the spleen-tissue itself. More recent investigations[26] have shown that the spleen, like the liver and some other organs, contains special enzymes (adenase, guanase, and xanthin oxydase), by whose action the split products of the nucleins may be converted to uric acid, and it is probable, therefore, that this latter substance is constantly formed in the spleen. 4. Lastly, a theory has been supported by Schiff and Herzen, according to which the spleen produces something (an enzyme) which, when carried in the blood to the pancreas, acts upon the trypsinogen contained in this gland, converting it into trypsin." The latter is treated at length under the next heading.

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[26] Consult Jones and Austrian: Zeit. f. physiol. Chem," Bd. xlviii, S. 110, 1906.

The statement that the spleen contains, as do other organs, such ferments as adenase, guanase, and xanthin oxydase is suggestive, in view of the fact that they are all oxidizing ferments. This fact is all the more interesting in that, as shown below, it is the plasma alone, *i.e.*, plasma deprived of its red corpuscles which circulates in the intercellular spaces of the pulp-cords.

An incidental remark of Professor Mall's, in the contribution previously referred to, goes far toward demonstrating that I have not erred so far in ascribing to the blood-plasma *per se* the active part in the blood's function. This constitutes such a far-reaching feature of this entire work that the following lines appear to us as timely: "The microscopical anatomy shows that the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease and granules only with difficulty. In life *the plasma* constantly flows through the *intercellular spaces* of the pulp-cords, while the *blood-corpuscles keep within fixed channels.* Numerous physiological experiments which I have made corroborate this view." If this can occur in the spleen it is doubtless possible elsewhere in the organism, especially when we consider that red corpuscles average in diameter about $^1/_{3000}$ of an inch, while the lumen of the majority of functional capillaries is less than one-half that size. Of course, corpuscles adjust themselves to the dimensions of the structures surround them; but it is apparent that in many instances—the tortuous capillaries of pericellular net-works, for instance—such a system could but compromise the free circulation of the fluids, and, simultaneously, the functional efficiency of the organ itself.

THE SPLENO-PANCREATIC INTERNAL SECRETION.

From the data already submitted as to the functions of, and the functional relationship between the spleen and pancreas, it is evident that each possesses its own complete mechanism, and that *in both organs, as elsewhere in the economy, the oxidizing substance (adrenoxidase) or the blood containing it is the source of functional activity.*

Still, have we any reason to believe, with Popelski, that it is through oxidation that the intrapancreatic trypsinogen becomes converted into trypsin? Can we say, for instance: the intrapancreatic conversion of trypsinogen into trypsin is not effected by the splenic ferment, but by the oxidizing substance, when the efferent vagus nerves transmit appropriate impulses? We think not, much as such a process would coincide with the multiple functions that we have already ascribed to the oxidizing substance.

We have seen that when the pancreas becomes functionally active its arterioles are caused to dilate by their vagal nerve terminals, and that the speed of the blood-flow through the organ is increased. Yet, while the net-work of capillaries is very rich, these *encircle* the secreting lobules, and, though in close relation with the glandular epithelium beneath the basement membrane, they in no way, as in the spleen, break up into reticulated tissue wherein their blood is poured; they merely lapse, as elsewhere in the organism, into venules, which ultimately carry the blood to the larger venous channels. Blood and trypsinogen do not come into contact, therefore, in the ducts of the typical pancreatic lobule: that which text-books employ to illustrate the origin, centripetal migration, and functional elimination of the zymogen granules. These are lost in the lobular lumina and ultimately reach the greater duct on its way to the intestine, without apparently having come into contact with the oxidizing substance.

But, this being the case, how can we account for the experimental evidence adduced by Schiff and Herzen and other physiologists who have confirmed their work? How can we explain, for instance, the digestion of 17 grammes of albumin in 7 hours with pancreas obtained from a normal cat and *no* digestion in 12 hours with pancreas from one in which the vessels of the splenic hilum had been ligated: an experiment repeated many times, and always with identical results?

It is evident that, if—as believed by Schiff and Herzen—the circulatory cycle must be traversed by the splenic ferment before the pancreas can be influenced by it, this ferment will merely pass *through* the pancreas without in any way converting trypsinogen into trypsin, and fruitlessly re-enter the splenic venous current. There being no connection between blood-stream and trypsinogen and none between the latter and the splenic ferment, we are now reduced to either deny the need of any converting agency, and simultaneously close our eyes to all the experimental data adduced,—including Popelski's, which sustain the existence of *some* process which has imposed the necessity upon him of accounting for *results* witnessed,—or seek elsewhere for an explanation of the phenomena recorded. Thanks especially to the labors of Langerhans,[27] Laguesse,[28] and Opie,[29] this task will be greatly facilitated.

Laguesse having studied the islands of Langerhans in the pancreas of an adult man (an executed criminal) and of a child which has died several hours after birth without having taken nourishment, and in the sheep, reached the following deduction, quoted from one of our own reviews of his work.[30] "Long before the pancreas begins its function as a digestive gland granules of secretion accumulate in the internal zones of the cells; and, when these come *into contact with the blood,* a portion of them appear as though dissolved, while in others the granules are resorbed. It might be supposed, with some reservations, that an internal secretion always exists in the cell,—very much developed, however, and preceding the external secretion in the fœtus. Later, each cellular group would be first full, then acinous, furnishing alternately an internal and an external secretion." Opie refers to the observations of Kühne and Lea[31] in injected specimens, in which these investigators "found scattered through the organ glomerular structures composed of dilated and tortuous capillaries, and showed that these glomeruli correspond to the cell-groups which Langerhans described. The islands are penetrated by numerous wide, tortuous capillaries, which lie between cells, forming irregular, anastomosing columns. Material injected into the *duct* of the gland does not penetrate the islands." The view that the islands of Langerhans furnish an internal secretion is indirectly sustained, and the histological topography outlined seems to furnish a clue to the mechanism involved: *i.e., the existence of two sets of glands capable of yielding similar products, but adjusted individually, as regards distribution, to the needs of two systems: the digestive system and the circulatory system.*

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[27] Langerhans: Inaugural Dissertation, Berlin, 1869.

[28] Laguesse: Comptes-Rendus Hebdom. des séances et mémoires de la Société de biologie, Paris, No. 28, 1893.

[29] Opie: Johns Hopkins Hospital Bulletin, Sept., 1900.

[30] Laguesse: "Annual of the Universal Medical Sciences," vol. v, 1894.

[31] Kühne and Lea: Untersuch. a. d. Physiol. Inst. d. Univ. Heidelberg, ii, 488, 1882.

To develop this proposition and that on page 379, we will employ the excellent paper of E. L. Opie,[32] in which the entire subject is not only reviewed, but also greatly elucidated through personal investigations. The quotations from his article will be limited, however, to the features bearing directly or indirectly upon the question in point, as given in the above italicized lines:—

"Schäfer and Diamare think that the vascular islets probably furnish an internal secretion. The only evidence in support of this suggestion is contained in the short preliminary notice of Ssobolew. He states that after feeding animals on carbohydrates the cells of the islands become more granular. After ligating the duct of Wirsung in dogs, the islands of Langerhans, he finds, are not involved in the sclerotic process which follows. He thinks that this fact explains the absence of glycosuria after ligation of the pancreatic ducts. In human cases I had observed after duct obstruction similar resistance of the islands to the consequent inflammation. In pancreases of two diabetics Ssobolew was unable to discover islands of Langerhans.

"In the human pancreas the islands were found to be more numerous in the splenic end, or tail, than elsewhere. To obtain a numerical statement of their relative abundance, their number was determined in a sectional area of 0.5 square centimeter. Sections about 10 millimeters thick were made from the enlarged duodenal portion of the pancreas, or the head; from the midportion, or body; and from the splenic end, or tail. The following table gives their number in an area of 0.5 square centimeter in sections taken from the head, body, and tail of ten normal organs:—

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[32] E. L. Opie: *Loc. cit.*

TABLE I.

	HEAD.	BODY.	TAIL.
I	14.0	13.0	30.0
II	39.0	25.0	42.0
III	4.0	4.0	19.0
IV	4.0	10.0	43.0
V	27.0	18.0	59.0
VI	25.0	27.0	26.0
VII	18.0	18.0	29.0
VIII	6.0	10.0	29.0
IX	44.0	32.0	61.0
X	14.0	23.0	32.0
Average	18.3	18.0	34.0

"The table shows that the islands are more abundant in the tail, or splenic end, than in the head and in the body, where they are present in approximately equal number. They are almost twice as numerous in sections from the tail as in those from other parts. Since the number in only one plane is recorded, in order to obtain their actual relative abundance it is necessary to square these figures. They are then found to be slightly less than three and a half times as numerous in the tail as elsewhere.

. . . .

"The cells composing the islands resemble those of the acini. They have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body. The basal zone of the secreting cell, as is well known, stains deeply with nuclear dyes,—for example, hæmatoxylin or methylene blue,—while the central portion, which contains zymogen granules, remains unstained. The cells of the island, however, do not stain with nuclear dyes, while with eosin their protoplasm takes a homogeneous bright-pink color. The nuclei differ but little from those of neighboring acini. They vary considerably in size, and not infrequently one finds very large, round, vesicular nuclei whose diameter is two or more times that of those about. Occasionally the cells, forming columns between which are the anastomosing capillaries, are very closely packed together, and nuclei are situated almost side by side; more frequently the cells of the island are less numerous and the nuclei are less closely crowded together.

"The outline of the island is usually round or oval, and is not infrequently accentuated by a delicate circle of fibrous tissue. In other instances the outline is less sharp, and the body accommodates its shape to that of the neighboring acini. Occasionally one sees, apparently within the island, cells arranged, as in the acini, about a central lumen, and, indeed, in many instances it is difficult to convince one's self that they do not form part of it. The impression is produced that the columns of the island are in continuity with cells having an acinar arrangement. Since the islands and the secreting acini have a common origin, it is not inconceivable that they may occasionally remain continuous in the adult organ. When the fœtal pancreas is affected by congenital syphilis, the islands, I have found, retain their continuity with the secreting structures.

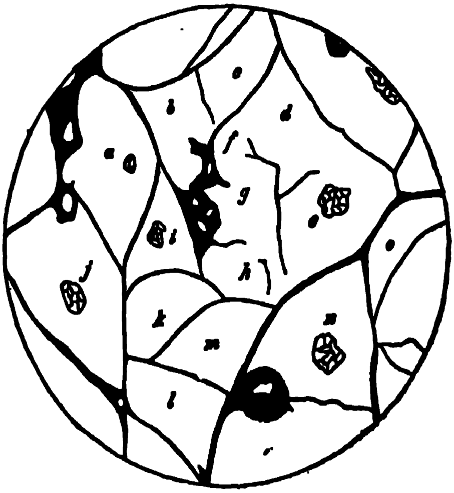
"In the human pancreas the groups of acini about terminal ducts are not sharply defined by connective tissue; so that individual lobules, as in the human liver, are indistinctly marked off and in places apparently fuse with one another. In the pancreas of the cat the lobules, like those in the liver of the pig, are much more sharply outlined by interstitial tissue. Details of structure have been studied in the pancreas of the cat.

"The parenchyma is divided by septa of fibrous tissue into small polygonal areas in size and shape. When injected with Berlin blue, a small ramification of the ducts is found to penetrate the isolated group of acini. These subdivisions, or lobules, often appear completely isolated by fibrous tissue from those near by, but when one of them is traced through a series of sections its separation may be uniform, and in places one finds the parenchyma of adjacent lobules in contact, the dividing septa being incomplete. That these polygonal structures are actually independent of one another and represent units of structure is readily demonstrated by causing an inflammatory increase of the interstitial tissue. If the pancreatic ducts of a cat are ligated and the animal killed at the end of two or three weeks, the gland is found to be the seat of a chronic interstitial inflammation, characterized by an increase of the interlobular tissue. The lobules are completely separated from one another by narrow bands of firm, fibrous tissue, and occur in sections as rounded, triangular, or polygonal areas of parenchyma.

"The islands of Langerhans occupy a position near the center of the lobule, and in the splenic end of the gland each lobule contains an island. In a given section many lobules whose limits are more or less distinctly outlined are seen to contain islands situated near their center, while in neighboring lobules such structures may not be discoverable. If, however, serial sections are studied, every lobule is found to contain an island. Its presence within the lobule is not constant in other parts of the organ, and in the extremity of the descending arm of the gland they are very few in number.

"The lobules are grouped about the medium-sized ducts. The main ducts give off branches approximately at right angles to their course. Branching one or more times, a duct forms the center of a group of lobules, which is usually elongated in form and tapers to a point at or near the surface of the gland. Such lobule groups are separated from one another by relatively wide bands of areolar tissue much looser in texture than that separating the individual lobules. The lobule groups in the fresh state or in tissue macerated a few days in Muller's fluid may be separated from one another by careful teasing. In the loose tissue lie the larger ducts, arteries, veins, and nerves. An artery and vein penetrate each lobule group in company with the duct, and ramify between its lobules. The smallest arteries occasionally penetrate the lobules, but usually branches, diminishing in size, give off capillaries which enter the lobule and form a close net-work between the gland-acini.

"The capillaries of the island of Langerhans form a glomerulus of tortuous, freely-anastomosing vessels, much thicker than those between the acini. A single afferent vessel like that of the glomerulus of the kidney does not enter this group of dilated capillaries, but numerous anastomoses make it continuous with the interacinar capillaries. When Berlin blue is injected through the aorta into the arteries of the pancreas, it not infrequently happens that in portions of the gland which are poorly injected the vessels of the island are filled with the injected mass, while the surrounding capillaries are, for the most part, empty. If instead of soluble Berlin blue a granular injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the interacinar capillaries contain little of the injected material. The glomerular net-work is in very free communication with the smallest arteries, and apparently has a richer blood-supply than other parts of the lobule.



CAMERA-LUCIDA TRACING OF THE LOBULE BOUNDARIES IN ONE OF A SERIES OF SECTIONS FROM THE SPLENIC END OF A CAT'S PANCREAS.

The majority of the lobules are well defined. Those marked *d*, *e*, *f*, *g*, and *h* are poorly outlined, but are found to be more readily distinguishable when traced through the series of secretions. The lobules, which are lettered (*a* to *o*), were traced through the series, and each was found to contain an island of Langerhans situated near its center. The section passes through the island in lobules *a*, *e*, *i*, *j*, and *n*. (*Eugene L. Opie.*)

"In the human pancreas lobules and lobule groups are not so regularly arranged as in the cat. But both structures are more or less clearly definable. The lobules vary much in size, and are usually not clearly separated from one another. Though an island of Langerhans is often situated in the center of a more or less clearly defined lobule, no constancy of position is discoverable. The lobule groups are separated by relatively wide bands of loose areolar tissue in which are contained the medium-sized ducts, the blood-vessels, and the nerves. Within a lobule group the arteries and veins, which are side by side, do not, as in the cat, accompany the ducts."

The multiplicity of facts reviewed in the foregoing pages and the intricacy of the whole question make it necessary to collate and group in logical sequence the salient features of each subject discussed, in order to render a fruitful comparison of their merits possible. Not only are we required to analyze the questions involved in the light of the solid data that the last forty years have furnished,—*i.e.*, since Schiff first studied the relations between the spleen and the pancreas,—but all these must likewise be sustained by, and be in accord with, the functional mechanisms of the organs involved as I interpret them if my own views are well founded. If they are, they must necessarily assist us greatly in elucidating the various problems, physiological and pathological, to which reference has been made, since the very elements which they introduce bear upon a predominating factor in all these processes: *i.e.*, oxidation. To this subdivision of the subject we will, therefore, turn our attention.

Can we ascribe to oxygen, or rather to the oxidizing substance of the blood, the conversion of pancreatic trypsinogen into trypsin? We have seen that in both the spleen and pancreas the oxidizing substance seems, as elsewhere, to play the main functional rôle; the extrinsic and intrinsic vessels are disposed in a similar manner as regards their nervous relations, and vasodilation calculated to increase the flow of blood through both organs is similar. Moreover, we have seen that in the spleen the dilation incident upon malarial intoxication could be traced to the adrenals,—the primary source of excessive oxidation,—while in toxic glycosuria we obtained as clear evidence that overactivity of the pancreas could also be ascribed to these organs. Again, the ease with which oxygen is thought to convert trypsinogen into trypsin—a mere current of oxygen through a solution of zymogen sufficing to produce trypsin—has been fully emphasized. Besides Heidenhain's labors in this connection, we need but recall Schiff's experiment with the two halves of a pancreas, one of which was infused at once and the other left exposed to the air a day, with the result that the latter alone proved active; and also that of Herzen, in which an infusion of active spleen mixed with an infusion of inactive (hence zymogen-laden) pancreas proved very active, while a pancreatic infusion mixed with one of inactive spleen digested nothing. Heidenhain ascribed to oxidation the conversion into trypsin, in this experiment. Indeed, when we consider the wealth of oxygen in the blood supplied the pancreas, direct from the lungs via the cœliac axis, it would seem as if it should be the predominating factor of the conversion processes involved.

And yet, the oxidizing substance being a constituent of the blood-plasma, it would have to penetrate into the ducts *per se* and *as* oxidizing substance in order to carry out the required reaction. There is no evidence that a direct channel, such as there is in the spleen, by means of which the capillaries directly pour their blood into the secreting structures, exists. As may be seen in the annexed illustration, the splenic vessels actually terminate in the latter; "their walls become much attenuated, lose their tubular character, and the cells of the lymphoid tissue of which they are composed become altered, presenting a branched appearance and acquiring processes which are directly connected with the processes of the sustentacular cells of the pulp."[33]

Nor is there evidence that canaliculi such as those of the hepatic cell exist by means of which the blood-plasma or its contents may directly find their way to a structure corresponding to bile-channels, which in the pancreas would be represented by the ducts. Langerhans long ago demonstrated that canaliculi were present in the lobules between the epithelial cells, but these, besides being pyriform, terminate as blind pouches, with their orifice directed toward the glandular lumen. Saviotti also found these minute, delicate, pouch-like channels. Ramón y Cajal, using the Golgi method, found that they sent offshoots into the cells themselves, but that these also ended as blind pouches, their ampullar dilations never reaching beyond the line which separates the granular portion of the cell from the clear area. It is evident that these constitute collecting channels for the products of glandular metabolism: a further indication that no free channel between the blood-stream and the ducts exists.

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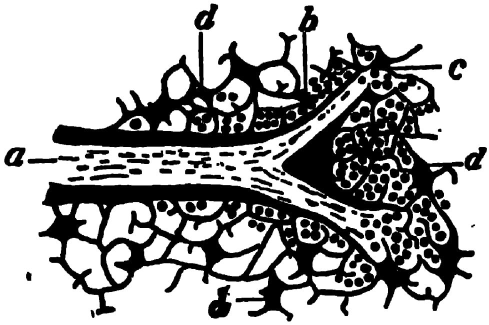
[33] Pickering Pick and Howden: "Gray's Anatomy," 1901.

Indeed, experimental proof to this effect is available: When the histological examinations of Kühne and Opie were mentioned on page 394, it was noted that material injected into the *duct* of the gland did not penetrate the islands of Langerhans. If, on the other hand, Opie's observation that injections of Berlin blue often filled the vessels of the island *per se*, leaving the majority of surrounding capillaries empty, is considered in this connection, it is evident that there can be no direct communication between ducts and blood-stream through either the islands of Langerhans or the glandular lobules that contain them. This involves an all-important deduction, however, viz.: that the splenic ferment, as well as the oxidizing substance, merely passes through the pancreas in transit, the latter, in its usual capacity of reagent, being intended only to activate function.



TERMINATION OF SMALL BLOOD-VESSELS IN THE SPLEEN. (*Gray.*)
a, Small artery. *b*, Vessel undergoing lymphoid change. *c*, Vessel continuous with supporting cells. *d*, Supporting cells.

But how, under these circumstances, can we account for the experimental results reached by Schiff and Herzen, Heidenhain, Lépine, Pachon and Gachet, and Popelski? All these observers in one way or another have unquestionably shown a direct relationship between the blood-serum and trypsinogen, Heidenhain and Popelski considering oxygen as the converting agency, with solid experimental data to sustain them; Schiff, Herzen, and the other investigators mentioned attributing to the splenic ferment the same mission, with equally strong experimental backing. How account, for example, for the results observed in the following experiment of Herzen's? Two fasting dogs, having received all the meat they could eat, were at once submitted to ligation of the pylorus, bile-duct, and jejunal end of the duodenum, and also, in one of the dogs, of the hilum of the spleen. Albumin having been introduced into the duodenum, both dogs were killed after seven hours. In the dog with ligated splenic hilum the albumin was intact; in that in which the splenic vessels were free, the albumin had disappeared. This and other experiments to which we have referred may, indeed, be said to prove—whichever be the prevailing converting agency—that a communication between the blood-channels and the ducts exists.

We have seen that there is no evidence to show that the acini in direct communication with the ducts also open into the blood-vessels; these, as elsewhere, form a close-net-work around the acini, but they do not open into the blind pouches of the latter. Could the communicating channels traverse the islands of Langerhans? That these organs do not possess such channels or even ducts has been shown by Dogiel,[84] who studied this question in a well-preserved human pancreas treated by the chrome-silver method, and in which the gland-ducts, "even in their finest intra-alveolar branches, were well stained." Yet these structures possess morphological characteristics that are suggestive. Dogiel, for example, found that they possessed relatively large capillaries located in the cellular trabeculæ. All investigators seem to agree upon the unusual size of those vessels. Kühne and Lea define the islands as "glomerular structures composed of *dilated* and tortuous capillaries." Opie calls them "vascular islets" which are in "very free communication with the smallest arteries and apparently have a richer blood-supply than other parts of the lobule." That these dilated arteries are possessed of special functions is suggested by the fact that, "if, instead of a solution of Berlin blue, *a granular* injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the intra-acinar capillaries contain little of the injected material." They appear to constitute alveoli or ampullæ rather than true vascular channels, in which what blood passes through them is submitted to some kind of process.

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[84] Dogiel: Böhm and von Davidoff, *Loc. cit.*

An interesting feature in this connection was noted by Opie, viz.: the fact that the cells of the islands of Langerhans are in some instances continuous with the regular glandular elements of the organ, in such a manner as to prolong the ducts of the latter by encircling them. "Occasionally," says the author, "one sees, apparently within the islands, cells arranged, as in the acini, about a central lúmen, and, indeed, in many instances, it is difficult to convince one's self that they do not form part of it." This intimate relationship between the two sets of glandular elements is further emphasized by the manner in which their capillaries are related. While the smaller arteries or arterioles ramify between the lobules and supply the net-work of capillaries to the acini, they also communicate with the tortuous and dilated vessels of the islands of Langerhans; so that the latter, as regards their vascular relations, really constitute glomerular expansions and offshoots of the regular acini's blood-channels. We thus have two sets of superposed glands around a common duct, the upper, or common acini, pouring their own secretion (or granules) into it through their microscopical ducts; the lower, those of the islands—possessed of no ducts or other orifices—presenting their dilated capillaries or alveolar walls so as to cause them to face, and perhaps slightly project into its lumen. If we now replace by an active circulation through all these vessels the cinnabar or ultramarine-blue injections referred to above, the accumulation of the latter in the islands distinctly points to a similar process during life: *i.e.*, accumulation of blood and its normal result (with narrower blood-vessels at each end of the glomerulus): *i.e.*, centrifugal pressure.

If we now conjoin Opie's remark—"the impression is produced that the columns of the island are in continuity with cells having an acinar arrangement"—and Mall's observation, in his study of the microscopical anatomy of the spleen,—that "the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease . . ."—it seems probable that we hold the key to the situation. Indeed, what have we in the dilated glomerules of capillaries of the islands of Langerhans but vascular ampullæ? Centrifugal pressure under the circulatory conditions mentioned can have but one result: *i.e., filtration of the blood-fluids through the ampullar walls and into the ducts.*

It is, perhaps, unnecessary to point to the fact that, besides being the only functional mechanism warranted by the anatomical structures present, it also meets all the requirements of the well-founded experimental data adduced. The precision with which it seems to harmonize the two seemingly antagonistic features of the general function represented—*i.e.*, the Schiff-Herzen spleno-pancrèatic process and the Heidenhain zymogen-oxidation process—is also noticeable. If it is also realized that all these elements of the general function now fall sequentially in the normal order of their physiological usefulness, it will become apparent that I must have reached a solution—that submitted below—worthy of confidence:—

1. The splenic ferment secreted into the splenic vein is carried to the portal vein and by this vessel through the liver, thence by the hepatic vein to the inferior vena cava, and after passing through the cardiopulmonary circuit is distributed throughout the entire organism.

2. The quantity of splenic ferment distributed to the pancreas is proportionate to the amount of blood carried thereto by the pancreatic subdivisions of the splenic artery, and represents but a fraction of that supplied to the general circulation.

3. The splenic ferment distributed to the pancreas follows the course of its blood-channels, and is distributed to the cellular elements of the organ dissolved in the blood-plasma.

4. On reaching the cellular elements, the plasma, through its *oxidizing substance (adrenoxidase), insures functional metabolism of both glandular structures present,—the lobular acini and their immanent structures, the islands of Langerhans,—which metabolism, during the passive, or inactive, state of the organ, ends in the formation of the secretion granules.*

5. When at the end of the fourth hour of general digestion the pancreatic ferments are required in the intestinal canal, the vagus incites, sustains, and governs the functional activity of both the pancreas and the spleen, and thus insures their synchronous action as long as the pancreatic ferments are needed.

6. Intrinsic-nerve (vagal) dilation of the arterioles that supply both the pancreatic lobules and the islands of Langerhans with capillaries constitutes, as elsewhere, the mechanism through which glandular activity is sustained; but, the islands' vascular ampullæ possessing no muscular layer, they become the seat, owing to their large size, of sufficient blood-pressure to cause the blood-plasma and its contained splenic ferment and oxidizing substance (adrenoxidase) to filtrate through their walls.

7. Some lobules are entirely composed of true secreting cells; others contain, besides, islands of Langerhans. In the latter lobules the secretion, therefore, consists of two different bodies: the granules of the true secreting cells and the blood-plasma derived by filtration from the islands.

8. The true secreting cells and those of the island being in continuity and surrounding a common lumen (Opie), both bodies—(1) the zymogen, or trypsinogen-forming, granules, and (2) the plasma containing the splenic ferment and the oxidizing substance (adrenoxidase) meet in this common lumen, which connects with the terminal ramifications of the pancreatic duct.

This is about as far as we can proceed at present, since we can only surmise that, as soon as the products referred to meet in the glandular lumen, the splenic ferment at once converts the trypsinogen granules into liquid trypsin. Interesting in this connection, however, is the fact, observed by Laguesse, that "long before the pancreas begins its functions as a digestive gland granules accumulate in the internal zones of the cells; and when these come into contact with the blood a portion of them appears as though dissolved." As is well known, this is precisely what happens even in true acini that do not belong to lobules supplied with islands. When secretory activity occurs, the granules of the inner zone of the cells simply disappear in the central lumen; but how and in virtue of what agency they are transformed into secretion at this point has not been determined. In the lobules supplied with islands of Langerhans the effused serum more than satisfies this feature, since it supplies two agencies thought to be capable of converting the granules into trypsin; but what of the lobules deprived of islands? How are *their* granules converted?

To answer these questions we must first ascertain which of the ferments credited to the pancreas can be shown to originate in the true acini. We have seen that, when the hilum of the spleen is ligated and no splenic ferment can find its way to the blood, the digestion of albumin ceases. It is, therefore, evident that, in accordance with Herzen's view, the splenic ferment is a *sine qua non* in the process through which trypsinogen is converted into trypsin. But why does the oxidizing substance not continue the conversion after ligation of the splenic hilum? There is but one answer to this, viz.: Herzen's zymogen and trypsinogen are not similar bodies; while zymogen is converted into some pancreatic ferment by oxygen, trypsinogen is not, and always requires the splenic ferment.

To illustrate this fact we submit, *in extenso,* two of Gachet and Pachon's experiments, performed to show that it was the spleen's ferment, and not its hæmoglobin, that converted protrypsin, which they term "proferment." Believing that zymogen, which, as shown by Heidenhain, is very greedy for oxygen, and "proferment" are the same bodies, their aim is to prove that, injected in arterial blood, pancreatic ferments cannot be converted into trypsin therein. But, interpreted from our standpoint,—since the blood contains oxidizing substance which zymogen would readily take up,—these experiments prove that zymogen and their proferment (trypsinogen) differ, as stated.

"As the proferment of the pancreas becomes very easily transformed into trypsin under the influence of oxygen," say Gachet and Pachon, "it seems possible that splenic extracts, intensely colored by the hæmoglobin, should owe their trypsinogenous power to the fixed oxygen of hæmoglobin which they hold in solution. If such is the case, arterial blood, richer in oxygen, should render a pancreatic infusion containing the proferment more active than venous blood. A. Herzen has already studied this question and antagonized it by means of appropriate experiments. On our side, we have tried to ascertain the value of this opinion in the following manner:—

"*Experiment II.*—The pancreas of a fasting dog was allowed to macerate two hours in ten times its volume of a saturated solution of boric acid. By decantation, 200 cubic centimeters of the maceration liquid were taken and distributed among four flasks: A, B, C, and D.

"To A were added 20 cubic centimeters of defibrinated *arterial* blood (obtained from the fasting dog).

"To B were added 20 cubic centimeters of defibrinated venous blood (obtained from the fasting dog).

"To C were added 20 cubic centimeters of *congested* spleen (aqueous maceration).

"To D were added 20 cubic centimeters of distilled water.

"These flasks, in each of which was introduced 1 cubic centimeter of albumin, were then placed in the oven at 39° C.

"At the end of 4 hours beginning digestion was observed in flask C; villosities appeared on the surface of the cube of albumin, which continued to be attacked in an energetic manner.

"A and B, after remaining in the oven 24 hours, did not show very clear traces of digestion. Their cubes of albumin presented slightly less sharp projections, and their angles were more rounded. The cube in flask D was slightly attacked.

"*Experiment III.*—The pancreas of a fasting dog was divided into three parts and triturated: the first alone; the second with 20 cubic centimeters of femoral arterial blood; the third with 20 cubic centimeters of venous blood, taken, as was the former, from a fasting dog. These were placed in flasks A, B, and C, containing each 150 cubic centimeters of boric-acid solution. After remaining 2 hours in the oven the peptonizing power of the decantation liquids was tried. Their proteolytic action was very slow; the first signs of digestion had appeared: in A after 16 hours of oven; in B and C after 20 hours. Digestion was not further advanced in the flask containing arterial blood than it was in that containing venous blood.

"It can be seen that in these two experiments arterial blood showed itself as inactive as venous blood. One cannot, therefore, ascribe the unquestionable action of the extract of congested spleen upon the pancreatic proferment to the oxygen of splenic tissue."

There is one feature in this connection, however, which requires elucidation: the influence that the use of *fasting* dogs might have had on the experiments. We have seen that under these conditions suprarenal activity becomes reduced; the blood may, therefore, contain but a minimum of oxidizing substance. Herzen performed an experiment which not only confirms our conclusion that zymogen and trypsinogen are not identical bodies, but also shows that fasting does not influence the results just given. As Herzen's experiment has already been reviewed at length, we will only reproduce its salient points. The pancreas of a fasting dog (hence rich in trypsinogen and other ferment-forming agencies) was infused in glycerin, and this in turn was mixed with eight samples of blood (bled directly in double its quantity of glycerin), four being taken from a fasting dog and four from a dog in full digestion with its spleen greatly dilated. The four samples were taken in both animals from the femoral artery, the femoral vein, the splenic artery, and the splenic vein. Fibrin was then added to each sample. "After 1 hour there was still no trace of digestion under the influence of the femoral blood, arterial or venous, nor of the splenic arterial blood of the fasting dog; first traces of digestion were beginning to manifest themselves under the influence of the splenic *venous* blood of this animal. Digestion was rather advanced in the case of the femoral arterial and venous blood and splenic arterial blood of the *digesting* dog; the fibrin had almost entirely disappeared under the influence of the *splenic venous* blood of the same animal." This seems to us to confirm not only the view held by Herzen, that the splenic ferment is the only agency capable of converting trypsinogen into trypsin, but also that trypsinogen does not, like zymogen, possess affinity for oxygen.

This may be further demonstrated by showing that oxygen does exist in the blood, and that if we were dealing with zymogen it would be oxidized therein. The oxidation of sugar converted from glycogen, we have seen, represents the main factor in the production of functional energy in the muscles and other structures. That sugar occurs in the blood normally, but in small quantities, its combustion therein depending mainly—as in toxic glycosurias—upon suprarenal activity, we have also seen. The more these organs produce of their secretion, the greater is the proportion of oxidizing substance in the blood, and suprarenal insufficiency means a corresponding increase of sugar in the blood through imperfect oxidation. Hence the oxidizing substance is a sugar-destroying agency.

That an agent capable of consuming sugar exists in the blood was ascertained by Lépine in 1889, who named it "glycolytic enzyme." Howell, referring to this substance, says: "It has been asserted by Lépine and Barral that there is normally present in the blood an enzyme capable of destroying sugar. Their theory rests upon the *undoubted fact that sugar added to blood outside the body soon disappears.*" This obviously constitutes another proof of the existence of oxidizing substance in the blood.

Howell, referring also to the supposed source of Lépine's glycolytic enzyme, says, referring to the pathogenesis of glycosuria: "The most plausible theory suggested is that the internal secretion produced contains a special enzyme, glycolytic enzyme, whose presence in the blood is necessary for the consumption of sugar. Such an enzyme *may be obtained from the blood,* but it is not proved whether it is a normal constituent or whether it is produced after the blood is shed by the disintegration of some of its corpuscular elements." . . . "It is interesting and suggestive to state, in this connection, that post-mortem examination in cases of diabetes mellitus in the human being has shown that this disease is associated in some instances with obvious alterations in the structure of the pancreas." That the glycolytic enzyme is, as oxidizing substance, a normal constituent of the blood is obvious; but the interesting feature to determine now is whether, as believed by Lépine, the pancreas is the source of the ferment, since, if it were, it would constitute an additional factor in this organ's physiological functions.

To which of the two pancreatic active structures can we hypothetically ascribe the formation of the glycolytic enzyme? Laguesse[85] has ascribed this function to the islands of Langerhans. That these structures underlie some physiological process in addition to that already analyzed by us is undoubted. The fact that they contain large nuclei shows that they are physiologically active. "The cells composing the islands resemble those of the acini," says Opie; "they have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body." They must produce some ferment or its zymogen, for Ssobolew found that feeding animals on carbohydrates caused them—*i.e.,* their protoplasm—to become granular. This is indirectly confirmed by the fact that these bodies are often found diseased in diabetes. They had entirely disappeared in two of Ssobolew's cases. In a case of Opie[86] hyaline metamorphosis was strictly limited to the islands of Langerhans the glandular acini remaining intact. Flexner[87] refers to this cause of diabetes as follows: "That it depends upon an internal secretion supplied by the pancreas to the blood is highly probable. Whether this hypothetical secretion is the product of the cells of the islands of Langerhans is unproven."

The data bearing upon this source of diabetes are very few,—an unfortunate fact, since these particular structures seem to us to play the predominating rôle in the production of glycosurias of pancreatic origin, now that we have ascertained that they are, through their ampullæ, the only thoroughfares for the splenic ferment. Still, can we, with Laguesse, now consider them as the source of a glycolytic ferment? Were we to admit this possibility, we would find ourselves obliged to concede that the pancreas supplies the intestinal tract with a glycolytic ferment besides an amylolytic ferment, and we would have, as a result, the formation of maltose from food-starches and its immediate destruction by the glycolytic ferment, thus annulling the very important functions of sugar in the economy.

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[85] Laguesse: *Loc. cit.*

[86] Opie: Journal of Experimental Medicine, March 25, 1901.

[87] Flexner: University of Pennsylvania Medical Bulletin. Jan., 1902.

It is plain that the islands of Langerhans are not the source of a glycolytic ferment. Of course, Professor Lépine has never, that we know of, sustained this view, his contention being simply that the normal pancreas contains a glycolytic ferment which finds its way into the lymph and blood, in which it controls the consumption of sugar by the tissues. And his experimental evidence, in the light of our views, shows this to be the case, since it all goes to prove that the oxidizing substance which enters the pancreatic circulation is a glycolytic body. This does not mean that it acts therein as such; indeed, the organic cells at once take up its oxygen for their own functional interchanges, the blood returning to the splenic veins as venous blood. But it is nevertheless obvious that Lépine should have experimentally found, as he says, a glycolytic ferment in the pancreatic blood. All we show, therefore, is that Lépine's glycolytic ferment is probably the oxidizing substance.

But why should disease of the pancreas under these circumstances increase the proportion of sugar in the urine: a feature which Lépine ascribed to decrease of sugar destruction and to the fact that "these lesions decrease the source of the glycolytic ferment in the economy"? From our standpoint, of course, the adrenals are the original source of the oxidizing substance: *i.e.*, adrenal secretion *plus* oxygen. But does this account in an equally satisfactory manner for glycosuria? This introduces a very important feature of the entire analysis, one, indeed, bearing upon the pathogenesis of all forms of pancreatic diabetes.

We have previously referred to the fact that disease of the islands of Langerhans had been found to be a prominent causative factor of diabetes by various pathologists, and that Opie had witnessed a case in which these islands *alone* were diseased. This obviously points to the fact that, *if in accordance with our view the ampullæ of the islands are the pathways of the Schiff-Herzen splenic substance to the ducts,* we are dealing either with obstruction or impaired conversion of trypsinogen into trypsin, or both simultaneously. If, bearing this feature in mind, we review the list of pancreatic diseases that cause glycosuria, it will become apparent that these two factors account for the phenomena observed in many cases: calculi, lipomatosis, hypertrophy, tumors, induration, and periglandular sclerosis. Atrophy,—a condition which in itself implies functional impairment,—on the other hand, constitutes the majority of the remaining pathological processes encountered post-mortem in this organ.

But the question which now imposes itself is this: Why and how does a condition that interferes with the conversion of trypsinogen into trypsin or that impedes the passage of the latter to the intestinal foodstuffs cause diabetes? The answer now seems plain, viz.: *because insufficiency of trypsin is followed by imperfect reduction of proteids to simpler bodies, resulting in the formation, or inadequate splitting, of toxic albuminoids.* In other words, impaired pancreatic action of the kind mentioned gives rise to toxic glycosuria.

Our interpretation of the general subject seems again to conciliate antagonistic views. Indeed, while Lépine[38] has affirmed that "the pancreas exercised a glycolytic influence," Chauveau and Kaufmann have held the opposite: *i.e.*, that "glycolysis is not diminished in diabetes, and that diabetes is exclusively due to an increase in the production of glucose." We have shown that the arterial blood of the pancreas does contain a glycolytic body,—the oxidizing substance,—but we have also—by our analysis of Cartier's paper and other data—demonstrated that suprarenal overactivity was the underlying cause of toxic glycosuria: *i.e.*, a source of increased production of sugar. To further sustain this fact, we may recall that the coal-tar products, as already stated, possess a marked tendency to inhibit the functions of the adrenals, sufficiently, in some instances, to produce blood-disintegration. Lépine has himself observed that methæmoglobinuria could follow the use of antipyrin. This remedy is now classed among the most active agents at our disposal for the reduction of glycosuria. A remark of Professor Lépine proves this to be the case in another way. Referring to experiments conducted with the collaboration of Porteret, he says, regarding the action of antipyrin, that, "in the cases in which it exercises an antidiabetic action, this substance acts, not by activating the destruction of sugar, but *by preventing its formation*."[39] This is due, as explained in the second volume, to the fact that antipyrin excites a center (the sympathetic center, also described in the second volume) whose purpose is to cause constriction of the arterioles after, as we have seen, they have been dilated by a cranial nerve. Antipyrin thus produces general constriction of the arterioles, and the blood admitted into the adrenals, pancreas, and liver—the main organs involved in diabetes—being reduced, the "formation" of sugar is actually prevented.

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[38] Lépine: "Le Diabète," Paris, 1899.

In view of these facts, what is the nature of the product the existence of which the prominent nuclei and the granules observed in the protoplasm of the islands indicate? This is elucidated by two other features just brought out, namely: (4) that glycosuria may be the result of intoxication by toxic albuminoid bodies incident upon an insufficiency of trypsin, and (5) that disease limited to the islands, as shown by Opie, can cause glycosuria. It is plain that, in the latter case, the permeability of the ampullæ being alone compromised, the pancreatic lobules that contain no islands are free as to the elimination of their secretion into the ducts. If they produce trypsinogen,—*i.e.*, trypsin,—why are the functions of the latter inhibited or absent as indicated by the glycosuria? The only logical answer to this question is that *the islands of Langerhans alone secrete trypsinogen.*

This fact, when added to others reviewed, normally leads to another deduction: *i.e.*, that, in addition to any other function it may possess, *the spleen and the islands of Langerhans are functionally united in the formation of a ferment,—trypsin,—which is able to digest albuminoid bodies in the blood-stream.*

We can now readily understand why the spleen and the pancreas are so intimately connected through their nervous supply. Indeed, this throws light upon a phenomenon which we approach almost with diffidence: *i.e.*, Claude Bernard's experimental glycosuria obtained by puncturing the medulla oblongata. "That pathological conditions of the central nervous system and perhaps of the sympathetic and larger peripheral nerves may give rise to glycosuria and diabetes is, of course, established," says Flexner.[40] "The number of neuropathic conditions in which one or the other of these has been found is now considerable. The one definite condition, *the effect of which is constant,* is Claude Bernard's *piqûre,* and, as bearing out the physiological relationship existing between *certain unknown structures* in the floor of the fourth ventricle and the glycogen-store in the liver, may be cited the instances of lesions (hæmorrhages, softening, tumors) in man observed in this situation with which glycosuria has been associated. That cerebral and perhaps spinal disturbances other than those in the region of the fourth ventricle may be associated with or followed by diabetes many clinical cases prove. On the other hand, there is no evidence that would show that it is the direct influence of the central nervous system upon the carbohydrate metabolism that produces hyperglycæmia and glycosuria. Indeed, the experiments in which *the splanchnics were sectioned after piqûre* (Claude Bernard and others) *without producing glycosuria* show the necessity of the interaction of other organs."[41]

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[39] The italics are Professor Lépine's.

Read in the light of all we have said,—particularly the allusion to the relationship between the medulla and the suprarenal glands through the splanchnic,—these lines, from so competent an observer as Flexner, and which confirm those of Cartier as to the action of section of the splanchnic, seem to us to afford confirmatory evidence based upon the most solid labors of the last half-century and to embody Claude Bernard's own sanction. To analyze their far-reaching meaning would involve the repetition of what has been said in all this volume. Formulated as a deduction, the functional relationship between the floor of the fourth ventricle and glycosuria would be as follows: *Puncture of the floor of the fourth ventricle (Claude Bernard) causes glycosuria because the increased blood-supply in the injured area incident upon the local reparative process correspondingly excites the normal structures around this area. As*

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[40] Flexner: *Loc. cit.*

[41] All italics are our own.

these structures include nerve-fibers which govern the adrenals, these organs are stimulated and glycosuria is produced by their secretion.

What we might term the intrinsic functions of the pancreas have now been analyzed; the importance—also in conjunction with the spleen—of its *extrinsic* functions must now be inquired into. Foster states that "a pancreas taken fresh from the body, even during full digestion, *contains but little ready-made ferment,* though there is present in it a body which, by some kind of decomposition, *gives birth to the ferment.*[42] . . . To this body, this mother of the ferment, which has not at present been satisfactorily isolated, but which appears to be a complex body, splitting up into the ferment, which, as we have seen, is, at all events, not certainly a proteid body, and into an undeniably proteïd body, the name of *zymogen* has been applied. But it is better to reserve the term zymogen as a generic name for all such bodies as, not being themselves actual ferments, may by internal changes give rise to ferments,—for all 'mothers of ferment,' in fact,—and to give to the particular mother of the pancreatic proteolytic ferment the name trypsinogen." In other words, and in accord with prevailing custom, each zymogen is named from the ferment it produces: the zymogen of trypsin being "trypsinogen"; that of pepsin, "pepsinogen," etc. It is therefore permissible to use the term "amylopsinogen" as the main product of the true lobular acini to differentiate it from trypsinogen, the product of the islands of Langerhans, reserving the term zymogen as a generic term for all pancreatic ferments. As "zymogen" under these conditions, it preserves characteristics attributed to it by Heidenhain; it is soluble in water, in which it is split, after exposure to the air, into trypsin, etc. (Charles). The conversion of trypsinogen into trypsin has been ascribed to oxygen; but if my views are sound and the former is the normal product of the islands, the portion distributed through the pancreatic ducts is intimately combined with the splenic ferment in the ampullæ as fast as formed, so that it can never be obtained as trypsinogen. Hence, oxygen will split zymogen into trypsin, etc.; but trypsin is not oxidized trypsinogen.

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[42] The italics are the author's.

We have followed the course of the blood from the splenic vein and back again to the splenic artery which supplies branches to the pancreas, and we have seen that on its way through the latter the arterial blood surrenders its oxygen to the cells and its splenic substance to the islands. The dominant feature of the extrinsic functions of the pancreas is its power to destroy albuminoid toxic bodies, and it is evident that the splenic ferment, the mission of which is merely to unite with trypsinogen to form trypsin, cannot do this alone. It is *trypsin* that constitutes the antitoxic body, and it is the pancreas, therefore, that supplies it to the organism. How does it penetrate the general blood-stream?

Now that we have ascertained that the islands of Langerhans are the seat of manufacture, as it were, of at least a part of this antitoxic agency, and that it collects (combined) in the ampullæ, the manner in which the general circulation becomes supplied with it is clear: *i.e.*, the quantity that permeates through the ampullar walls is but a portion of their contents, and the rest is swept away with the blood and reaches the splenic vein through the pancreatic veins. But this does not mean that trypsinogen may not be carried alone in the same manner to the splenic vein and therein combine with the splenic ferment to form trypsin. In fact, this must constitute the prevailing process, if the anatomical distribution of the islands of Langerhans, as observed by Opie, can serve as guide.

As we have seen, Opie found that the islands of Langerhans were over three times as numerous in the splenic end of the pancreas as elsewhere, and that the part of the organ not in communication with the splenic vein—*i.e.*, the extremity of the descending arm—contained none. Moreover, each lobule in the splenic end of the organ was found to contain an island: a very suggestive fact. The tip of the pancreas, which is almost in contact with the spleen, thus marks the starting-point of the islands; so that trypsinogen begins to enter the splenic vein almost at the hilum. Pancreas and splenic vein being connected by several short venous radicles at about regular intervals, the blood in the vein must become literally saturated with trypsinogen, and its blood be replete with trypsin when it reaches the portal vein, during the active stage of intestino-portal digestion. We have seen in Herzen's experiment how rapidly albumin was digested with blood obtained from the splenic vein during this stage.

That the amylolytic ferment derived from Heidenhain's zymogen is also carried to the splenic vein is probable. I have shown that it was through the effects of this ferment that the liver glycogen was converted into sugar, and that the importance of the latter, when distributed to the muscles and other structures in which it is consumed, was very great. That the conversion of glycogen into sugar is a continuous process and that it is independent of digestion are recognized facts,—and necessarily so, since the activity of the functions that entail the use of glycogen may at any moment be increased, the tissues requiring replenishment to a correspondingly great degree at the expense of the liver reserve. How could this predominating function be carried on in the perfect manner that it is, were it connected with, or did it depend upon, any digestive process? Again, if present views prevailed and the amylolytic ferment were to only reach the liver after being secreted in the duodenum by the pancreas, then absorbed by the venules of the villi, how could we account for the conversion of glycogen between the periods of active digestion? That the intestinal tract is not the channel traversed by the portion of pancreatic amylopsin devolved to the conversion of glycogen into sugar is also suggested by familiar experiments.

We have seen that the insertion of a piece of pancreas into the tissues of an animal showing marked glycosuria, after removal of the pancreas, will cause it to disappear. This apparently constitutes a direct contradiction of all the foregoing statements; but such is not the case in reality. Minkowski[48] confirmed the fact, observed by other investigators, that glycogen quickly disappears after removal of the pancreas. This indicates two important features: *i.e.*, that glycogen is no longer formed after removal of the pancreas, and that some other agency converts it into sugar. Why removal of the pancreas should prevent the formation of glycogen may probably be accounted for by the fact that the absence of trypsin causes the digestion of albumins in the duodenum to cease, as shown in the Schiff-Herzen experiments. That the conversion of food-starches into maltose is also, owing to the absence of amylopsin, arrested, is evident. The only substitute for this ferment available is ptyalin; but though the salivary secretion—at least, its ptyalin—is quantitatively increased after removal of the pancreas, it is inadequate to convert all the starch required to compensate for the glycogen used. The glycogen, gradually converted by what ptyalin is swallowed with the saliva between meals, therefore disappears. The fact that ptyalin converts starch partly into dextrose greatly hastens the disappearance of the glycogen, the primary sugar of which is mainly maltose. It would seem, therefore, *that the glycosuria following extirpation of the pancreas is due to the action of ptyalin upon food-starches.*

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[48] Minkowski: Berliner klin. Wochenschrift, No. 5, 1892.

That the salivary secretion is gradually increased after removal of the pancreas is sustained by experimental evidence. Aldehoff[44] observed that glycosuria only appeared from 24 to 48 hours after the operation in turtles; in frogs it only appeared after four or five days, "slight at first, becoming more intense later on." Minkowski[45] found that it sets in after two or three days in dogs, under the same conditions. Again, during its passage through the stomach ptyalin acquires increased energy as a ferment. Charles[46] refers to this question as follows: "Chittenden and Griswold find that the presence of acid, as hydrochloric acid, to the amount of 0.005 per cent. decidedly increases the diastatic action, while an increase beyond this diminishes it, the action stopping with solutions of acid from 0.1 to 0.4 per cent.; the diastatic action of the saliva would, therefore, appear soon to cease in the stomach, but *the peptones* in that organ exercise a decided influence on salivary digestion, stimulating the ferment to *increased action,* particularly in presence of acid, which by itself may completely prevent the conversion of starch into sugar." Mering found that starch acted on by saliva yielded dextrin and maltose at first, then after some time grape-sugar.

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[44] Aldehoff: Zeitschrift für Biologie, Munich, Bd. xxviii, p. 293, 1892.
[45] Minkowski: *Loc. cit.*
[46] Charles: *Loc. cit.*

Yet, glycosuria so produced may, we have seen, be prevented by grafting a fragment of pancreas under the skin. Minkowski[47] grafted such fragments in the dog, cat, and pig, removed from the pancreas of these animals. When the graft had become adherent and functionally active, he removed the rest of the pancreas. No glycosuria appeared until the grafted portion itself had been removed. Besides indicating that ptyalin glycosuria prevails after resection of the pancreas, the fact that grafts can preserve normal functions clearly shows that the intestinal canal is not the only region wherein splitting of carbohydrates and proteids may occur. Each graft evidently received its blood through newly-formed vessels. This blood doubtless contained splenic ferment, since, as previously stated, the greater portion of this ferment really enters the general circulation *via* the liver, and ultimately reaches the portal circulation, probably by the hepatic artery, in the experimental animals. Such being the case, it is evident that *the splenic vein can, besides the intestinal villi, serve as a channel for the transmission of the pancreatic and splenic ferments to the liver.*

Here, again, however, we are brought to realize that the splenic ferment is not merely a local agency, but one which during spleno-pancreatic activity forms part of the entire blood-stream. I have given striking evidence of this in Herzen's experiment with blood taken from various arteries and veins. We saw that blood taken from the femoral vessels (arterial and venous) of a dog in full splenic digestion proved active in digesting albumin, and that the blood of the splenic vein was exceedingly active. Indeed, the blood which is so active in the pancreas originates from the cœliac axis, lungs, heart, etc.,—*i.e.*, from the general circulation,—and only contains the proportion of splenic ferment which the entire blood-stream contains. But a question suggests itself here: If, by the combination of trypsinogen and the splenic ferment, trypsin is formed, is it not trypsin-laden blood that re-enters the pancreas? Trypsin *would* re-enter this organ were the relative proportions of the two bodies not regulated by the vagus. As we find that a slight excess of splenic ferment will serve the physiological process in the pancreas,—to supply the intestinal canal,—if we grant the vagus even one-tenth of the truly wonderful prerogatives it seems to possess, we can readily assume that, by regulating the quantities of either ferment allowed to enter the blood-stream, it provides just the excess of splenic ferment in the pancreas to insure perfect function during the digestive process: all features which indicate that *trypsin is a constituent of the entire blood-stream when albuminoids are undergoing digestion in the alimentary channels.*

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[47] Minkowski: *Loc. cit.*

The far-reaching meaning of all this is suggested in the following deductions:—

1. *The cleavage processes to which trypsin submits albumins in the intestinal canal include the preliminary steps of a protective function.*

2. *The spleno-pancreatic internal secretion is represented by the trypsin which reaches the portal vein by way of the splenic vein, and which continues in the blood-stream the cleavage processes begun in the intestinal canal.*

3. *The main function of the spleno-pancreatic secretion, trypsin, in the blood-stream is to protect the organism from the effects of the toxic derivatives of albuminoid bodies of endogenous or exogenous origin, including toxins.*

Since the first and third conclusions were submitted by myself in the first edition of the present work (1903), they have received independent confirmation in many particulars through the researches (begun in 1905) of Abderhalden,[48] who concluded that "each separate cell, with very few exceptions, disposes of the same or similar ferments as those secreted by the digestive glands in the intestinal canal." He termed "defensive ferments," moreover, agents of this class which have for their purpose "to bring the so-called reactions of immunity into close line with processes that are normal and consequently familiar to the cells."

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[48] Abderhalden: "Defensive Ferments," third edition, 1914.

CHAPTER IX.

THE ADRENAL SYSTEM IN THE FUNCTIONS OF THE HEART AND LUNGS.

Reference has repeatedly been made to the functional connection between the secretion of the adrenals and the heart. Is this connection direct or is it indirect? In other words, is it the result of a direct stimulation of the heart-muscle such as is produced by suprarenal extract, or of the stimulating effect to which the increase of oxidizing processes, including those of the cardiac cerebro-spinal centers, give rise? Analysis of this question tends to show that both processes prevail simultaneously when from any cause the adrenals become over-active.

THE ADRENAL SECRETION AS THE SOURCE OF THE FUNCTIONAL ACTIVITY OF THE RIGHT HEART.

As freshly-oxidized blood is constantly being supplied to *both* sides of the heart, the specific action of digitalis upon the right heart to which I have referred cannot be ascribed to the oxidizing substance. Again, it would seem that the suprarenal secretion itself could hardly be credited with a local stimulating action upon the cardiac walls when the thickness of the myocardium is recalled, unless the latter be provided with channels calculated to insure the penetration of the secretion to its deeper tissues. Not only do such channels exist, however, but they are so disposed as to enable the adrenal active principle to permeate the entire myocardium and be equally distributed among the contractile elements. The channels to which I ascribe such important functions have been known as the "foramina of Thebesius."

These canals are described in Gray's "Anatomy" as follows: "The foramina Thebesii are numerous minute apertures, the mouths of small veins (venæ cardis minimæ), which *open* on various parts of the inner surface of the auricle. They *return* the blood directly from the muscular substance of the heart. Some of these foramina are minute depressions in the walls of the heart, presenting a closed extremity."[1] This information would afford but little light could we not supplement it with an excellent paper by F. H. Pratt,[2] in which the *nutrition* of the heart through the vessels of Thebesius and the coronary veins is studied. How much we are indebted to the author for his investigations is suggested by the following remarks: "So far as I have been able to determine, no *experimental* physiological work has ever before been done on the vessels of Thebesius; all opinion regarding their functional importance has rested upon the assumption that they only serve as veins, conveying a part of the venous blood from the coronary capillaries through the foramina Thebesii into the cavities of the heart."

After referring to the labors of Thebesius (1708), Vieussens (1757), Haller (1786), and Abernethy (1798), the author reviews the more modern investigations of Bochdalek,[3] which led to the conclusion "that the greater number of the small openings on the inner surface of the right as well as the left auricle, which from early times have borne the name of foramina Thebesii, represent the mouths of little veins that, *often uniting into larger vessels,* course with many branches *through the auricular walls.*" Langer's researches[4] on the foramina of the human heart are next analyzed. "With the aid of the blow-pipe, and by means of a watery injection-mass colored with Berlin blue, he demonstrated these foramina *in all the cavities* of the heart. He succeeded in injecting the vessels of Thebesius not only from the coronary vessels, but from the *endocardial* surfaces as well. Bochdalek's observations regarding the presence in both auricles of foramina Thebesii were thus confirmed, and the fact of a communication between the coronary vessels and each of the four cavities of the heart was thoroughly established. The foramina which Langer found on the endocardial surfaces of both ventricles were similar to those in the auricles, but much smaller. They were most conspicuous on the papillary muscles and in the *neighborhood of the great vessels,* being less easily seen in the region of the apex, where they were obscured by the trabecular net-work."

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[1] All italics are our own.

[2] F. H. Pratt: American Journal of Physiology, vol. i, p. 86, 1898.

[3] Bochdalek: Archiv für Anat. u. Phys. u. wiss. Med., Leipzig, p. 314, 1868.

[4] Langer: Sitzb. der k. Akad. der Wissensch. zu Wien, 1880, Bd. lxxxii, 3 Abth., p. 25.

Very suggestive in connection with my own views are also the observations of Gad[5] on the vessels of Thebesius in the ox, and to which Pratt refers in the following words: "In the method which he describes for demonstrating the action of the valves of the *left* heart, wherein water under pressure is made to fill the ventricle and aorta, he noticed that water flowed into the *right* heart from the foramina Thebesii. On illuminating the interior of the left ventricle he was enabled to see fine, blood-stained streams issuing from the endocardial wall into the clear water with which the cavity was filled." Finally he reviews the labors of Magrath and Kennedy,[6] who, "working with artificial circulations of defibrinated blood on the isolated heart of the cat, observed that a small portion of the *coronary blood* found its way into the *left ventricle.* The only possible source of access other than from the vessels of Thebesius was leakage past the aortic valves. This leakage, as shown by a manometer-record of aortic pressure, did not occur." The author closes his review of the literature of the subject with the statement that "notwithstanding these painstaking observations, the vessels of Thebesius still occupy a very obscure position in anatomical literature. Foramina Thebesii are referred to as constant in the right auricle, forming in part the mouths of small veins. Their occurrence in the left auricle is occasionally mentioned. But the fact that *the vessels of Thebesius open into all the chambers of the heart*—ventricles as well as auricles—is hardly recognized."[7]

In the author's own experiments, various agents were injected at a constant pressure, through the coronaries of fresh, often still living, hearts of the rabbit and dog. They showed that liquids in these vessels penetrate into the heart cavities through the endocardial foramina, thus verifying the foregoing data. As the cannula was tied directly into the artery, the liquid could only reach the cavities through the foramina, while in all experiments care was taken to avoid high pressures. In the heart of the ox the endocardial depressions were found "regularly *larger in the auricles* than in the ventricles," while in the right auricle "they may," he states, "be provided with thin, single valves, *especially about the origin of the great veins.*" In the left auricle the depressions are fewer in number and unprovided with valves. "Foramina Thebesii are *never absent from the ventricles,*" says Dr. Pratt. "In the *right* ventricle, which is *especially well provided with them,* the larger number are seen upon the septal wall. It is often *much more difficult to find them in the left ventricle,* although a diligent search is never without a reward" . . . "structures, accessory to these ventricular foramina, which might in any way serve the office of valves I have not seen." . . . "On the injection of the vessels of Thebesius with air by means of the blow-pipe applied to the foramina, characteristic, fine, *subendocardial ramifications,* which very frequently conduct the air into other Thebesian systems, or *even into the great coronary veins* will seldom fail to appear." The latter point is also sustained by experimental evidence.

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[5] Gad: Archiv für Physiologie, p. 280, 1886.

[6] Magrath and Kennedy: Journal of Experimental Medicine, vol. ii, p. 13, 1897.

[7] All italics are our own.

The fact that the right side of the heart is endowed with a more perfect system of canalization than the left is suggested by the following remarks: "The ease with which injections of air and blood could be made to demonstrate the connection between the vessels of Thebesius and the coronary veins caused me to doubt the opinion expressed by Langer that the foramina Thebesii in the ventricles *communicate with the veins by capillaries alone.* To settle this point, I injected the coronary veins of the ox with starch and celloidin masses, both too thick to pass the capillaries, and found that even these emerged from the foramina Thebesii of the right ventricle. So intimate a connection, however, between the coronary veins and the vessels entering the *left ventricle I have not yet been able to demonstrate.*" The author also says: "By means of a very successful corrosion preparation, made by injecting the veins of an ox-heart with celloidin, I was able to trace the communication. In this preparation the position of some of the foramina

Thebesii was marked by small disks of the hardened mass formed by the oozing out of the celloidin upon the endocardium. These foramina were shown to be connected with the smaller *coronary veins* by fine branches. The still finer ramifications which, as Langer has demonstrated, lead from the foramina and branch directly into capillaries were here uninjected; they would appear only when injected from the foramina themselves."

The only connection between the vessels of Thebesius and the coronary arteries that he could find, notwithstanding repeated attempts, was by capillaries. Bochdalek having observed that the foramina of one auricle communicated with those of the other, he was able by blow-pipe injection to verify the correctness of this view, the air of one auricle having passed out through a similar exit into the other.

To sustain his view that the nutrition of the heart may be carried through the vessels of Thebesius some time after the coronary arteries are absolutely obliterated, a number of experiments are related. Thus, fluid introduced into the ventricle of an isolated heart, by means of a cannula passed down to this cavity, and tightly held *in situ* by a ligature passed around the auriculo-ventricular groove, only found its way through the vessels of Thebesius. Defibrinated blood, inserted into the organ through this cannula, brought on, often within one minute, "strongly marked, co-ordinated contraction of the ventricle." As the blood thus introduced would become venous, the action would become gradually reduced, but renewal of the blood would at once cause the heart to resume its normal action. "With a periodic supply of blood," says the author, "and with favorable temperature and moisture this may continue several hours." That mere mechanical stimulation by distension did not cause the phenomena witnessed is demonstrated by the alternate use of Ringer's solution and defibrinated blood. While the solution failed to sustain contractions, blood always succeeded.

Another experiment served to demonstrate that a true circulation could take place between the vessels of Thebesius and the coronary veins. The organ being disposed as stated above, two of the coronary *veins* were incised; "a small, but steady, stream of venous blood issued from them." Under the same conditions the descending branch of the left coronary *artery* was opened. "No flow of blood occurred from the artery, although there was a free escape from an incision in an accompanying vein." In still another experiment the trunks of both coronary arteries were ligated and the ligature around the ventricles omitted. "The supply-cannula was tied into the ventricle through the oarta. On the introduction of blood the left ventricle alone began to beat strongly and regularly . . . the blood found its way in part into the right ventricle, coming of necessity through the walls. . . ." The blood from the left ventricle had thus found its way into the right one. Finally, he refers to the striking analogy which this nutritional system presents to that of the frog and cat. In the frog the heart is almost entirely nourished "through the branching passages that carry the blood from the interior of the heart nearly to the pericardial surface."

On the strength of all this evidence, Dr. Pratt concludes (giving only the features that bear directly upon the question we are analyzing) that: "1. The vessels of Thebesius open from the ventricles and auricles into a system of fine branches that communicate with the coronary arteries and veins by means of capillaries, and with the veins—but not with the arteries—by passages of somewhat larger size. 2. These vessels are capable of bringing from the ventricular cavities to the heart-muscle sufficient nutriment to maintain long-continued, rhythmic contractions. 3. The heart may also be effectively nourished by means of a flow of blood from the auricle back into the coronary sinus and veins." The author concludes with the very appropriate remark: "It is evident that the nutrition through the vessels of Thebesius and the coronary veins must modify in no slight degree the existing views of the nutrition of the mammalian heart, and of the manner in which infarction of the heart takes place." The clinical features of this question will be considered elsewhere.

Viewed from my standpoint, *the vessels of Thebesius are more concerned with the dynamics of the heart than with the nutrition of this organ,* though the latter function is not to be ignored, particularly in the sense emphasized by Pratt: *i.e.,* as a source of compensation. That nutrition of the left heart, auricle and ventricle, constantly filled with arterial blood, can result from a flow of the latter through the Thebesian vessels seems clear, but nutrition can hardly be associated with a similar process in the *right* heart, with nothing but *venous* blood to propel through the Thebesian channels. That nutrition, the recognized prerogative of arterial blood, owing to its oxygen, cannot be the active factor here is evident.

The right heart seems, judging from the anatomical arrangement of the parts concerned in the process, to play a physiological function of a special kind. While the Thebesian openings are larger in the auricles than in the ventricles, in the left auricle they are also fewer than in the right; but even more suggestive is the fact that, while some openings in the right auricle are supplied with valves, none have been found in those of the left. Again, both ventricles are supplied with foramina; the right ventricle is particularly well provided with them, while they are difficult to find in the left one. That the septal wall should show them most clearly on the right side is also suggestive. Evidently a similar condition exists between the auricles, as suggested by Bochdalek and confirmed by Pratt; but the fact that limited information supplied by works on anatomy usually covers only those of the right auricle points to greater prominence of the latter. Thus, Gray[8] states that the venæ Thebesii open "on the inner surface of the right auricle." Finally, the openings supplied with valves are in the right auricle, as we have seen; but they are also stated to be most conspicuous in the neighborhood of the great vessels; hence it must only be the Thebesian openings around the great vessels of the right auricle—the venæ cavæ and the pulmonary artery—that are provided with valves.

If we can now ascertain whether the current which enters the Thebesian vessels from the right auricle is shut *out* in this location, or secured *within* the channels, according to the manner in which the valves close,—*i.e.*, inwardly or outwardly,—we will be able to decide whether *venous* blood from the venæ cavæ or arterial blood from the lungs circulates in the Thebesian system.

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[8] Gray: "Anatomy;" edition, 1901, p. 622.

Bochdalek found that many of these openings in the auricles "presented the appearance of blind depressions, since they were often covered with single valves in such a way as to resist investigation with the blow-pipe" . . . "some were slit-like, resembling the mouths of the ureters; still others were large, round depressions, with smaller openings at the bottom." The first remark suggests that the openings serve as exits into the auricle, while the second points to the contrary, since it is difficult to conceive of a *depression* with "openings at the bottom" as a valve calculated to resist liquids exerting pressure on the concave side. From the left auricle Gad caused water to pass out of the right and left ventricular walls, but, as the auricular openings have no valves, this only serves to emphasize the extensive canalization which the Thebesian system represents. The system might, therefore, be considered as essentially calculated to distribute venous blood from the right auricle to the entire heart: a fact which the free anastomosis with the venous channels would seem to sustain.

Pratt states that he has seen "structures accessory to these *ventricular* foramina which might in any way serve the office of valves" . . . "the edge of the foramen is usually sharply defined and may frequently exist as a partial, *shelf-like,* covering, giving the impression perhaps of an attempt at a membranous valve; but it is seldom more than this." A shelf means a projection, and the fact that it is membranous suggests that during ventricular *contraction* this valve is pressed against the opening and closes it: a feature which involves the possibility that during diastole a current—whether venous or arterial—flows into the ventricle through its foramina. That the latter and their valves open inwardly—*i.e.,* in the ventricle—is demonstrated by Pratt's experiment, in which he injected the coronary *veins* with starch and celloidin and found that even these passed *into* the ventricle. If, therefore, the venous blood of the right heart at all enters the muscular *walls* it is not through the foramina of the ventricle, *i.e.,* from below; it must be through the openings above, *i.e.,* those in the right auricle. The experiment in which the cannula was tied in the pulmonary artery, the blood being "allowed to enter the right auricle through insufficiency of the tricuspid," appears to us to further sustain this fact. The heart continued "its rhythmic contractions for eight hours: a period considerably in excess of that observed in nutrition through the vessels of Thebesius alone. It was inferred that blood had gained access from the auricle to the coronary veins and had thus aided materially in the nutrition." While this course may have been taken by some of the blood in the experiment, it is obviously not a normal one during life, and the unusual duration of the contractions seems to us to indicate that the blood that penetrated into the right auricle found its way into the Thebesian system *vià* the openings in this auricle, thus approximating as nearly as possible normal conditions.

The relations between the coronary veins and the Thebesian channels are self-evident, excepting, however, a theoretical back-flow from the auricles into the veins suggested by Pratt, which appears to us abnormal; at least it is not compatible with our views of the process. The Thebesian vessels and coronary veins were found to communicate freely on the right side, but not on the left, with the ventricular foramina. The septal foramina were also found to communicate with the coronary vein at the end of the sinus. An interesting feature is the fact that blood passed into the right ventricle flowed freely from a cut vein of the *left* heart (experiment of April 3, 1897). On the other hand, the relations between the coronary arteries and the Thebesian vessels are of a peculiar kind; thus the communication between the *left* coronary artery and the *right* ventricle seems as free as that between the same artery and the *left* ventricle (through the Thebesian channel) is limited. The experiment in which a colored solution was passed into the left coronary artery caused an accumulation of 400 cubic centimeters to flow from the right ventricle, while only 1 cubic centimeters flowed from the left, sufficiently emphasizes this fact. Haller, who had observed that injected substances flowed out freely from the surfaces of both ventricles, states that "the passage from the arteries into the cavities of the left side is more difficult."

All these features seem fully to supply the needs of the function with which the secretion of the suprarenal glands must be connected, if the phenomena witnessed in many disorders and after the use of most remedies have been correctly interpreted. That we are in the presence of a dual process of which the suprarenal secretion, operating in the right heart, and the arterialized blood in the left heart are active factors seems probable. Again, the marked power of arterial blood —or rather of plasma—since the defibrinated blood filtered through cotton was used—to sustain functional activity, even when only poured into the ventricles, as shown by Pratt, certainly indicates that the blood must alone be able, during life, to compensate, in case of need, for insufficiency of blood furnished by the coronary arteries.

The contractions of the *left heart* seem to me to be greatly assisted by the arterial blood that enters it, and mainly by that which enters the cavities themselves. The experiments of Pratt having shown that contraction could be produced by contact with arterialized blood, the arrival into the *auricle* of a normal quantity of this fluid must be fully capable, therefore, of causing contraction of the walls of that cavity. The relations of the several structures and the mechanism involved are in all probability as follows: The main structures upon which the arterial blood reacts are (1) the musculi pectinati and (2) the sinus venosus and appendix auriculæ, all of which are so disposed as to offer as much surface as possible to the blood. The walls of the cavities mentioned are provided with numerous channels, the Thebesian "veins," to satisfy this purpose. The blood which enters the auricle when it is dilated penetrates all the circuitous areas around the musculi pectinati and into the Thebesian vessels, and the ensuing contraction forces the blood-plasma into the smaller subdivisions of these vessels, from which they find their way into the auricular veins. When the arterial blood reaches the *ventricle*, a process similar to the preceding occurs. The columnæ carneæ are disposed so as to offer considerable surface to the blood, while the ventricular walls are permeated with Thebesian channels, into which the blood penetrates during diastole. The contraction induced closes the apertures of these channels, and forces the blood-plasma into their smaller ramifications and finally into the veins. The larger channels carry the corpuscular elements to the latter. The rôle of the coronary arteries will be referred to later on.

The *right heart*, as I view the process, owes its functional activity mainly to the suprarenal secretion brought to the cavities by the vena cava. I have sufficiently emphasized the power of this agent to restore cardiac action and sustain it even when the entire spinal cord has been obliterated. The manner in which it exercises its powers is similar to that of the arterial blood on the left side. On penetrating the auricle the contractile structures are submitted to its immediate effects; but the orifices of the Thebesian vessels or channels are more numerous and larger than in the left auricle. The membranous edges previously referred to as valves by the investigators quoted do not appear to me to merit being considered as such after careful examination of these structures in the ox-heart. The aperture being closed by the least squeezing of the tissues containing them, it seems evident that they should as readily close under the powerful contraction of the auricular tissues. The right ventricle also presents a very much larger number of Thebesian orifices than the left, while its walls, though thinner, plainly show the ramifications of these channels. That the venous blood charged with suprarenal secretion should at once penetrate the latter when the ventricle begins to contract is self-evident. Return of the blood to the circulation is effected in the same way as in the case of the left heart: *i.e.*, through the coronary veins.

The whole process is an exceedingly uncomplicated one, but, as we shall see later on, it simplifies many obscure problems, while affording, in connection with the coronary arterial blood, a supply in keeping with the vital importance of the organ itself. Again, Dr. Pratt's experiment, in which blood injected into the *left* auricle flowed freely from the right ventricle, emphasized the possibility of compensation in case of need. Thus, while under normal conditions, the pressure in both ventricles must be equal, reduced contraction—of the right ventricle, for example—through insufficiency of the adrenals would automatically cause the arrival into it, through the Thebesian foramina of the septum, of at least some arterial blood. That this does not always suffice to maintain interventricular equilibrium, however, is illustrated by the dicrotic pulse, the pulsus paradoxus, and kindred phenomena.

Suggestive in this connection are the remarks of Professor Porter in his review of the subject of cardiac innervation in the "American Text-book of Physiology"[9]: "A positive demonstration that the nerve-cells in the heart are not essential to its contractions," says this observer, "is secured by removing the tip of the ventricle of the dog's heart and supplying it with warm defibrinated blood through a cannula tied into its nutrient artery. Long-continued, rhythmical, spontaneous contractions are thus obtained (Porter[10]). As the part removed contains no nerve-cells, the observed contractions can only arise in the muscular tissue, provided we make the (at present) safe assumption that the nerve-fibers do not originate impulses capable of inducing rhythmic muscular contractions." In other words,—and this may be said to apply to all muscular elements including those of the muscular coats of the stomach and intestines,—the cardiac muscle is endowed with the inherent power to contract, even small detached pieces, when placed in appropriate media being capable of doing so. In the body, indeed, this contractile power is merely, so to say, kept active, and Porter remarks—almost prophetically in the light of our views: "The demonstration that the nerve-cells are not essential to contraction places us one step nearer the true cause of contraction. It is some agency *acting on the contractile substance.*[11] Evidence is accumulating that this agent is a *chemical substance,* or substances, *brought to the contractile matter by the blood.*"

That the "chemical substance brought to the contractile matter by the blood" is represented by the adrenal secretion and the oxidizing substance seems clear. Brown-Séquard over fifty years ago urged that the inferior vena cava contained *some* undetermined substance which contributed to the heart's dynamism.

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[9] Porter: "American Text-book of Physiology," second edition, 1900.
[10] Porter: Journal of Experimental Medicine, vol. ii, p. 391, 1897.
[11] All italics are our own.

THE ACTION OF THE ADRENAL SECRETION AND THE OXIDIZING SUBSTANCE UPON THE CARDIAC MUSCLE.

The histology of the myocardium still offers a broad field for conjecture, notwithstanding the many investigations to which it has been submitted by modern observers. The known facts are briefly these: Its tissue is composed, in man, of short, round fasciculi, or bundles, of striated fibers, possessed of thick lateral projections. The latter directly connecting with a similar projection of the adjoining bundles and being cemented to it, a thick close-meshed net-work is formed: a characteristic of the heart-muscle. But it differs from other muscles in several other particulars; its fibers are one-third smaller and their striæ are much more faint; they possess no sarcolemma and are, therefore, exposed to the immediate action of any fluid that may surround them. The manner in which the contractile structures are combined in bundles is also peculiar: each bundle is made up of central prismatic fasciculi of round fibers, in which nuclei (one or two) with their surrounding protoplasmic area are imbedded, the whole being surrounded with flat or ribbon-like columns of muscle-fibers. The perinuclear protoplasm referred to generally contains fat-droplets and *minute pigment-granules* which resemble hæmoglobin, and sends projections between the surrounding muscular fibers so that each of the latter is connected with and is only separated from its neighbor by a layer of protoplasm. This arrangement does not in any way modify the manner in which the sarcous elements are disposed, while the disks, clear spaces, etc., are precisely as they are elsewhere in the organism. These muscular "primary" bundles form, by their union with one or two of their neighbors, columns, or chains—or "secondary" bundles, which are covered, as shown by Ranvier, with a sheath of loose connective-tissue cells, which cells, in turn, connect with one another by numerous projections, or extensions. The primary fasciculi also contain connective-tissue sheaths which invest the muscle-fibers and are likewise supplied with connective-tissue cells. All this forms a close, though permeable, net-work, which makes it possible for a liquid to penetrate the muscular columns or chains and come into direct contact with the bare, or exposed, muscle-fiber.

Indeed, the intimate structure of the myocardium precisely supplies the required structure for the equable and free distribution of such an agency as the suprarenal secretion represents. Fluids can penetrate through the maze of cellular tissue to the bare muscular fibers; the sheaths that include the columns or chains of muscular bundles afford a peculiar system of canalization through which the liquids can easily gain access to them. These canals—the lacunæ of Henle—are the intervals between the columns of secondary bundles, or their sheaths, rather, which are placed in longitudinal apposition. Schweigger-Seidel and Ranvier having observed that interstitial injections of colored substances penetrated the lymphatic vessels, the lacunæ have been considered as adjuncts, or extensions, of the latter.

Renaut,[12] however, concluded that the penetration of the colored fluids into the lymphatics merely demonstrated the weak resistance of the endothelial coat of the latter, and the spaces, or lacunæ, of Henle being unprovided with endothelial walls, there was no ground for the prevailing belief that they represented lymphatic vessels. He found that all the lymphatic capillaries of the myocardium are located on the surface of the heart underneath the pericardium. They are large and bosselated and form a mesh-work which covers the whole cardiac surface, and send smaller blind pouches into the muscular interstices. The spaces of Henle should be considered, he thinks, "not as true lymphatic cavities analogous to those observed around the pulmonary lobules of certain animals, but as mere connective-tissue spaces, which represent, in fact, pathways for lymph." In a foot-note Berdal states that the spaces of Henle are crossed by "vessels," and in the text the following remark as to the identity of this lymph appears: "The muscular fibers of the heart are thus bathed in connective-tissue spaces in which lymph easily circulates; but this lymph is not that of the lymphatic vessels or capillaries, but that of loose connective-tissue spaces (Renaut)." It is needless to state that this suggests the presence of blood-plasma. Still, we can only consider this deduction as tentative.

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[12] Renaut: Traité d'Histologie pratique, p. 719; quoted by Berdal, loc. cit., p. 836.

The manner in which the blood-plasma, whether venous or arterial, is distributed by the Thebesian channels is well shown in a study of the vessels of the heart by Arthur V. Meigs.[18] The extreme paucity of literature on the Thebesian channels has caused them to be overlooked by practically all histologists; that they should be treated as capillaries in the author's paper is, therefore, as normal as it is for text-books to do so. "The capillaries of the human heart," says Dr. Meigs, "differ in two ways from those of other parts of the body: they penetrate the muscular fibers, and some of them are larger than those found elsewhere, and of different arrangement. . . . The accompanying illustrations are drawings which were made with the camera lucida. They are from sections of two human hearts. The first is from the heart of a negro woman, 40 years old, who died of burns. Some pieces of the organ were preserved in Fleming's solution, and others in 70-per-cent. alcohol, and they were stained in bulk with borax-carmine and imbedded in paraffin. The second heart is that of a man, 30 years old, who died of lead encephalopathy. When the post-mortem examination was made, the heart being still quite fresh, there was injected through each of the two coronary arteries as much as the blood-vessels would easily receive of a solution of 3 grammes of Berlin blue (Grübler's) in 600 cubic centimeters of water. Pieces of the organ of suitable size were at once placed in preservative fluid, some in 70-per-cent. alcohol, and others in formaldehyde solution. The tissue was afterward stained in bulk with borax-carmine and imbedded in paraffin.

"The penetration of the muscular fibers by the capillaries is made perfectly clear by the illustrations; it is shown as well by the injected as by the uninjected heart. The two methods of demonstration supplement one another, because, in injected tissue which has been stained, the blood-vessels and their situation are made very obvious by the contrast of color, but the details of the structure of the walls are obscured by the injection material, while, on the other hand, in the uninjected tissue, the structure of the blood-vessels can be seen with the utmost distinctness. In Figs. 1 to 4 the capillaries are easily recog-

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[18] Arthur V. Meigs: Journal of Anatomy and Physiology, Jan., 1899.

Fig. 1.

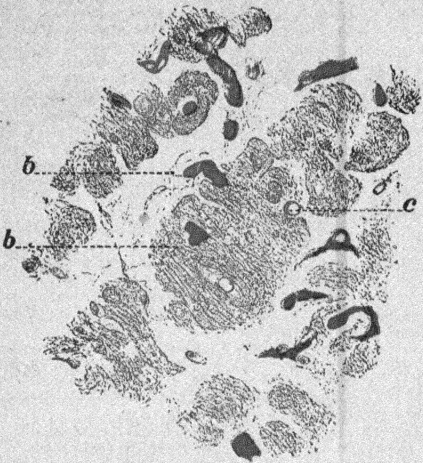


Fig. 2.

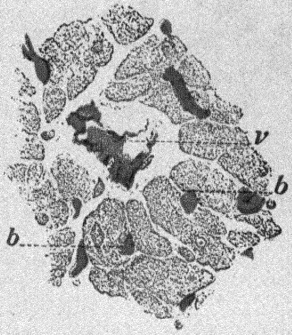


Fig. 3.

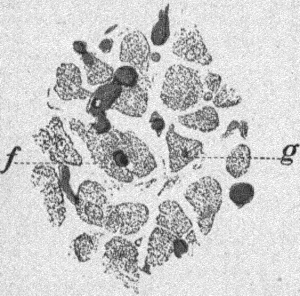


Fig. 4.

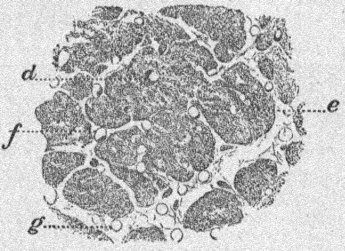


Fig. 5.

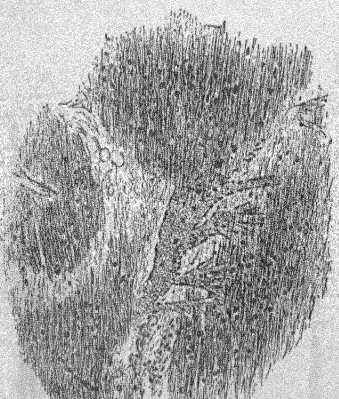
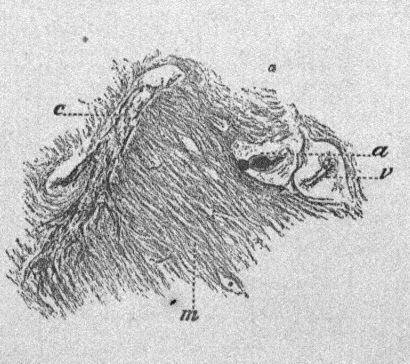


Fig. 6.



CIRCULATION OF THE HUMAN HEART. *[Arthur V. Meigs.]*

[Journal of Anatomy and Physiology.]

Fig. 1.

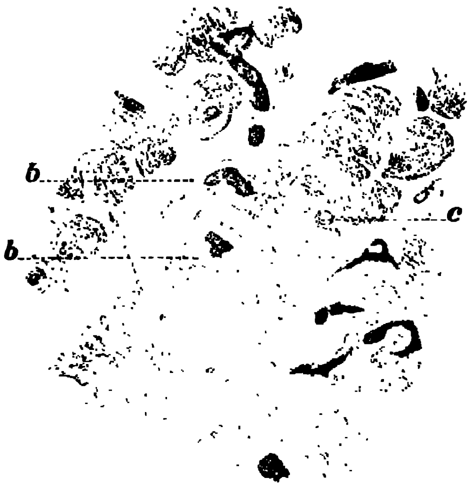


Fig. 2.

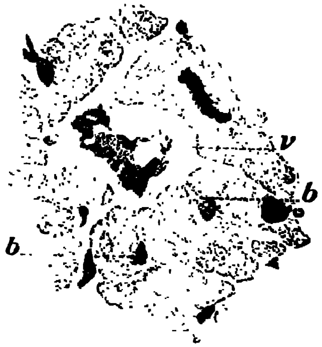


Fig. 3

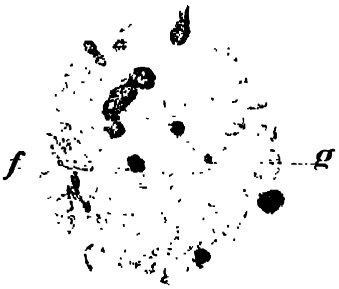


Fig. 4.

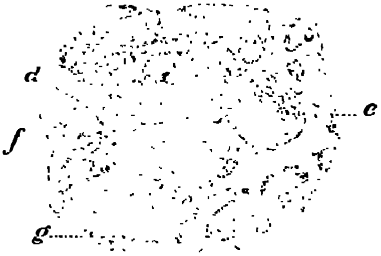


Fig. 5.

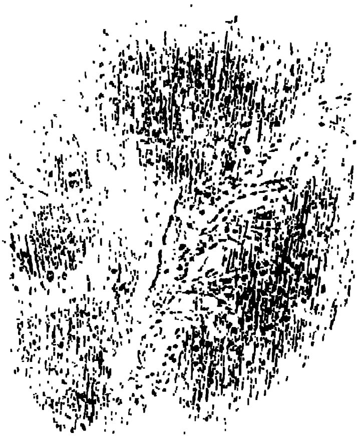
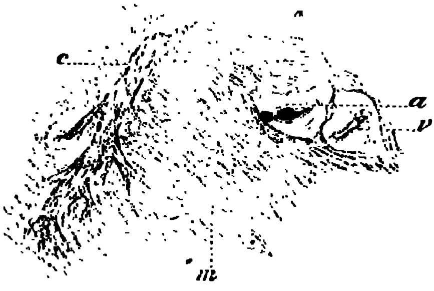


Fig. 6.



CIRCULATION OF THE HUMAN HEART. [Arthur V. Meigs.]

[Journal of Anatomy and Physiology.]

portions of the muscular substance of the heart, although it is well known that, upon the surface and in the connective-tissue interstices, arteries are found with their venæ comites, just as they are in other organs and tissues. The arrangement of the vessels upon the surface and in the interstices is in marked contrast with that found in the muscular substance proper. Here, when an arteriole is accompanied by an efferent vessel, this vessel is single coated and composed of endothelium, being exactly like the smallest capillaries, except in size. These peculiar large capillaries are found not only in company with arterioles, and, therefore, when carrying on the function usually performed by veins, but also alone.. When they are alone, it is impossible to be certain whether their function was afferent or efferent. It may well be that arterioles are less numerous in the heart than in other tissues, and that their place is taken by the large capillaries. These capillaries are so numerous and of such size that it seems likely they perform the function of reservoirs. The presence of the large capillaries and the penetration of the muscular fibers by the capillaries indicate a provision for the blood-supply of the heart even more bountiful than that of the other organs."

That these vessels are the Thebesian channels is evident; their mode of distribution and the peculiar endings of their subdivisions is particularly well shown in Fig. 6, while the outpouring of plasma for absorption by the muscle-elements is suggested by Fig. 5.

The fact that the distribution of the Thebesian channels is analogous to that observed in the heart of the frog has, we have seen, been noted by Pratt. This had also been noticed by Lannelongue, but this author considered the channels of the human myocardium as vestiges of the batrachian system. Berdal, who alludes to the latter, states that in the frog and in the batrachian *urodela* there are no ordinary blood-vessels. "The muscular fasciculi intercept cavernous spaces into which the blood penetrates directly and from which they are only separated by endothelium. *The frog's heart is thus a true sponge the structures of which, formed of muscular fibers, nourish themselves by imbibition.* In mammals, on the contrary, the myocardium contains distinct vessels. The capillaries form a net-work the meshes of which, elongated and parallel to the muscular fasciculi, are connected by short branches, which give each mesh the appearance of a parallelogram. When these vessels cross the spaces of Henle, they are covered, on the external surface, with flat connective-tissue plates." Pratt's observation not only includes the analogy between the human lung and that of the frog, but also with that of the cat, a mammal. Under these conditions, it becomes clear that in man, also, *the heart-muscle may be regarded as a sponge-like structure, the contractile elements of which are nourished and supplied with working energy by substances in the blood-plasma.*

What is the rôle of the blood of the coronary arteries in the functions of the heart? This may perhaps be traced by analyzing the effects of ligation of these arteries upon these functions. Porter[14] refers as follows to the experimental work in this connection: "The frequency of arrest after ligation is in proportion to the size of the artery ligated, and hence to the size of the area made anæmic, and is not in proportion to the injury done in the preparation of the artery. The circumflex and descendens may be prepared without injuring a single muscle-fiber, yet their ligation frequently arrests the heart, while the ligation of the arteria septi, which cannot be prepared without injuring the muscle-substance, does not arrest the heart. It is, moreover, possible to close a coronary artery without mechanical injury. Lycopodium-spores mixed with defibrinated blood are injected into the arch of the aorta during the momentary closure of that vessel and are carried into the coronary arteries: the only way left open for the blood. The lycopodium-spores plug up the finer branches of the coronary vessels. The coronary arteries are thus closed without the operator having touched the heart. Prompt arrest, with tumultuous fibrillary contraction, follows."

If the plasma that reaches the heart by way of the Thebesian channels can sustain both its nutrition and its contractions, how can such results as these be accounted for? The sudden arrest of the heart's action by plugging the coronary arteries certainly points to a predominating function, and, more than this, to a function of which they are alone the sources of blood-supply. That the rôle of the coronary blood is precisely that which obtains elsewhere in the organism is forcibly suggested by the experiments of Langendorff, who was able, according to Porter, "by circulating warmed *oxygenated defibrinated* blood through the coronary vessels, to maintain the hearts of rabbits, cats, and dogs in activity after their total extirpation from the body." It is clear that the blood-plasma can incite functional activity when introduced through the coronaries as well as when introduced into the ventricles. "Even pieces removed from the ventricle will contract for hours," continues the author, "if fed with blood through a cannula in the branch of the coronary artery which supplies them (Porter[15]). It is evident, therefore, that the cause of the rhythmic beat of the heart lies *within the heart itself,* and not within the central nervous system."

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[14] Porter: *Loc. cit.*

The italicized words represent precisely the factor of the problem which must be eliminated to enable us to differentiate the rôle of the coronary plasma from that of the Thebesian plasma, for blood will not alone induce contraction of the cardiac walls; almost any irritant will under appropriate conditions. Indeed, in the latter case it will sometimes undergo contractions without any external irritation; thus, "a strip of muscle cut from the *apex* of the tortoise ventricle and suspended in a moist chamber begins in a few hours to beat apparently of its own accord with a regular, but slow, rhythm, which has been seen to continue as long as thirty hours. If the strip is cut into pieces and placed on moistened glass slides, each piece will contract rhythmically. Yet in the apex of the heart no nerve-cells have been found" (Porter). Hence the power to contract is inherent in the contractile tissues, and subject, as elsewhere in the organism, to exacerbations of activity under appropriate stimulus. This fact being now established, our inquiry is simplified, since we need only to inquire into the nature of the processes through which it is utilized.

Analysis of the requirements of the right heart soon reveals the fact that the muscle-fibers require the same blood-supply that any muscle of the body does. Indeed, we then realize that the coronary arteries are their only source of oxygen. The venous blood that reaches it through the Thebesian channels has been depleted of this gas by the rest of the organism, and the suprarenal secretion, owing to its marked avidity for it, must, while in transit through the inferior vena cava, have deprived it of the little that might have remained in loose combination. We have reviewed the ultimate distribution of the coronary arteries as given by Berdal. It does not differ from that of other text-books. These generally concur in stating that the larger branches are distributed to the connective tissue between the large fasciculi, and once therein divide into arterioles, which, in turn, subdivide into capillaries that entwine the primary muscle-fasciculi. "The capillaries of the myocardium are very numerous," say Böhm and von Davidoff, "and so closely placed around the muscle-bundles that each muscular fiber comes in contact with one or more capillaries." Do they serve here, as elsewhere, to supply the muscle-fiber with its *source of energy*—*i.e.*, the carbohydrates that enter into the formation of the myosinogen—besides furnishing the oxidizing substance which sustains the combustion processes when brought into contact with this myosinogen? This is precisely where a difference between the muscular functions of the heart and those of other muscular structures appears to us to exist.

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[15] Porter: Journal of Experimental Medicine, vol. ii, p. 391, 1897.

There is practically no *passive* period in the heart's action when we consider that its stage of *activity* recurs every three-fourths of a sound; and the formation of myosinogen in its contractile elements, were it to proceed as slowly as it does elsewhere, would seem totally inadequate. Still, if the coronary blood is not endowed with the mission of supplying the heart-muscle with its source of energy, we are relegated to the venous blood of the Thebesian vessels and its suprarenal secretion for the myosinogen-forming products. A possible source of energy suggests itself when we consider that a carbohydrate known to react under the effects of the oxidizing substance is present in the hepatic veins,—*i.e.*, dextrose,—and that this sugar must pass through the right heart. As is well known, these veins carry their sugar to the inferior vena cava. That it is not used by the heart, however, was shown by a careful analysis of the whole question. This is submitted in the twelfth chapter. For reasons submitted in the second volume I was led to conclude that the minute granules referred to on page 433 were actually supplied to the heart through the intermediary of leucocytes. These cells were found to migrate from the liver (also through the hepatic veins) to the inferior vena cava, where they meet the adrenal secretion and proceed with it to the right ventricle. The evidence seems incontrovertible. The subject is so far-reaching, however, that it had to be considered separately. I shall, for the present only, refer to these granulations as "granules β" (Ehrlich). We now have, it seems to me, the elements necessary to account for the functional phenomena witnessed, namely:—

1. *The adrenal secretion, to contract the right auricle and ventricle and thus insure the penetration of the Thebesian blood into the cardiac walls* (which contraction venous blood or its contained granules β would not cause).

2. *The granules β, to account for the unusual and continuous production of energy which the heart converts into work.*

3. *A continuous supply of oxidizing substance via the coronary arteries to insure the combustion processes through which this energy is liberated.*

The annexed colored plate shows the manner in which the adrenal secretion and the granules β simultaneously reach the right auricle.

We can now understand why plugging of the coronary arteries should, as stated by Porter, arrest cardiac action. Referring to the effects of embolism and thrombosis of these arteries, this investigator also says: "That part of the heart-wall supplied by the stopped artery speedily decays. The *bloodless area* is of a dull-white color, often faintly tinged with yellow; rarely it is red, being stained by *hæmoglobin* from the neighboring capillaries. The cross-section is *coarsely granular.* The nuclei of the muscle-cells have lost their power of staining. The muscle-cells are dead, and connective tissue soon replaces them. This loss of function and rapid decay of cardiac tissue would not take place did anastomosis permit the establishment of collateral circulation between the artery going to the part and neighboring arteries. . . . The objection that one of the coronary arteries can be injected from another, and that, therefore, they are not terminal, is based on the incorrect premise that terminal arteries cannot be thus injected, and has no weight against the positive evidence of the complete failure of nutrition following closure." As I interpret the process, the absence of anastomosis further suggests the existence of an additional source of energy; but the cardiac arrest after ligation of the coronary also indicates that compensation from the opposite heart can only be gradually established. On the whole, the coronaries of the right side are as important as if they alone supplied the needs of the functions of that side. The granules β and the adrenal secretion are furnished to compensate for the absence of *arterial* blood in the right auriculo-ventricular cavities and in their Thebesian channels; but, the right coronaries being the only source of one of the three *necessary* factors of the process, their obliteration means as much as that of the left coronaries does to the left heart.

We can also understand why the contractile elements of the primary fasciculi are bare. They are constantly bathed in the plasma from which they obtain the granules β that enter into the formation of their myosinogen. The absence of oxygen in this fluid renders it perfectly harmless to the delicate structures that surround the primary and secondary bundles of muscle-fiber, and to the net-works of arterial capillaries that hug the bare fibers. The latter, by a rapid absorption,—which the presence of sarcolemma would counteract,—are constantly forming their products of metabolism: *i.e.*, myosinogen. The arterial capillaries, "coated, on their external surface, with flat connective-tissue cells" (Berdal), when they cross the spaces of Henle, being the only carriers of oxygen, normally become the active factors of nutrition and function. Their blood is the normal excitant—as elsewhere. The venous blood brings the granules β; the adrenal secretions, by contracting the cardiac walls, forces it into the Thebesian channels; the bare muscle-fibers absorb the granules and convert them into their own particular kind of fuel, myosinogen; the capillary blood supplies the energy for this metabolism—oxygen—and simultaneously sustains, again with its oxygen, the combustion processes upon which the continuous work of the organ depends. Here, as elsewhere, the potential energy of the chemical agencies present becomes converted into mechanical energy, which manifests itself as visible motion.

The left heart—the coronaries of which are larger than those of the right—presents anatomical features which modify, in a measure, the manner in which its physiological functions are performed. Both its auricle and ventricle containing arterial blood fresh from the heart, the Thebesian circulation does not appear to fulfill the primary rôle it does in the right heart. Indeed, the various experiments of Pratt and his predecessors and my own careful examination of the ox-heart distinctly show that the Thebesian circulation of the left heart, as regards intraventricular orifices, is much less important than that of the right heart. Still, the evident permeability of the interventricular septum and the histology of the left myocardium suggest that the left heart must receive material aid from the adrenal secretion and its granules β. This feature will again be referred to in the twelfth chapter.

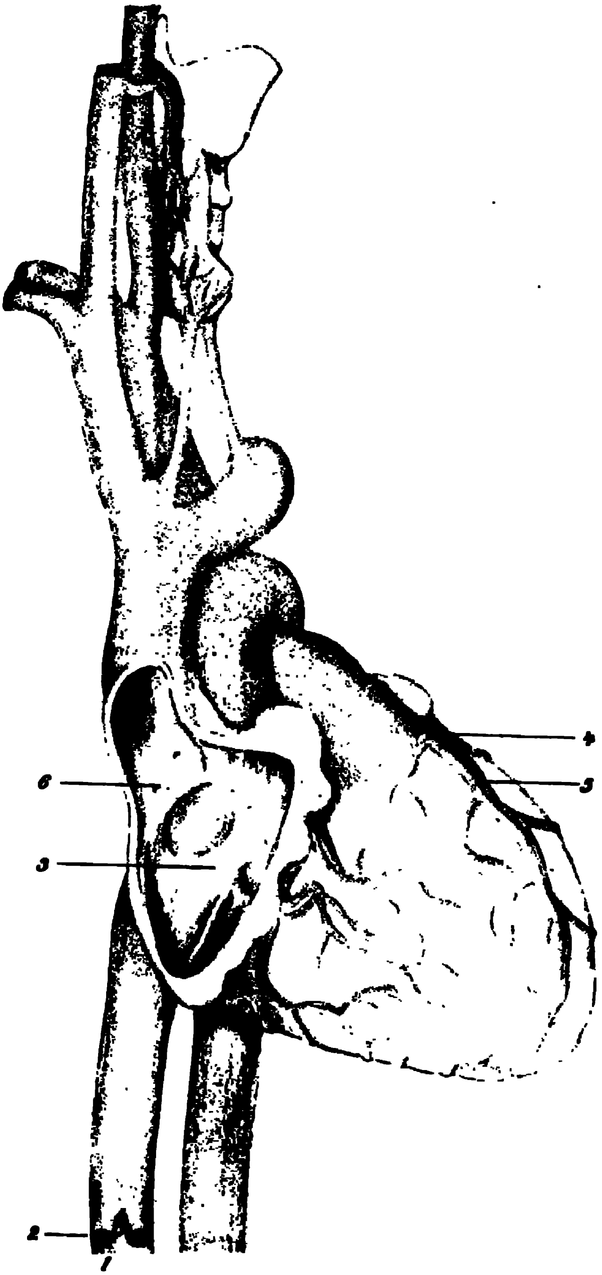
A feature that may be considered as demonstrated, and common to both sides, is the return of the blood, whether its source be the Thebesian or coronary systems, by way of the coronary veins. We have seen that Langer expressed the opinion "that the foramina Thebesii in the ventricles communicate with the veins by capillaries alone." My conception of the process involved would necessitate such an arrangement as regards the right heart. Indeed, so direct is this connection that even such viscid substances as starch and celloidin were found by Pratt, when introduced into the coronary veins of the ox, to emerge from the foramina Thebesii. Still, we could hardly expect such a free transit on the left side of the organ, inasmuch as the presence here of arterial blood only would suggest the presence of a structural organization similar to that of ordinary muscles. Indeed, referring to the vascular connections of the left heart, Pratt says: "So intimate a connection, however, between the coronary veins and the vessels entering the left ventricle I have not yet been able to demonstrate." Again, on the right side the connection with coronary veins must evidently be a physiological one, since "a small, but steady, stream of venous blood issued from them" when the veins were incised after the right ventricle had been filled with defibrinated blood.

But "no flow of blood occurred from the artery, although there was a free escape from an incision in an accompanying vein" in an experiment similar to that previously referred to, also performed by Dr. Pratt. In fact, it appears to me very doubtful whether even the capillary communication between coronary arteries and the Thebesian vessels, referred to by the latter observer in his conclusions, at all exists—at least in the walls of the right heart. Even disregarding my views, it seems evident that the admixture of venous blood with the arterial blood would greatly reduce and perhaps annul the functional efficacy of the latter as an oxidizing agent.

We can now understand how the adrenal secretion so greatly influences cardiac activity. An increase of it augments the force of the contraction, but the heart does not dilate as promptly nor perhaps as completely; hence its action is slower, but more forcible; we have seen that this represents the primary effect of all drugs sufficiently active to stimulate the adrenals. A still greater quantity of adrenal secretion increases the violence of cardiac action; the vessels are tense, and ecchymoses, hæmaturia, epistaxis, etc., may ensue. The heart acts normally, however, in the sense that its diastole is almost complete. Continuous cardiac stimulation through excessive production of adrenal secretion, due in turn to excessive production of iodothyrin, as in exophthalmic goiter, causes the heart to contract before it has exhausted its complete diastole and to work within a narrower field. Its contractions are sharp, but rapid: the type of the "cramped heart." Increase of adrenal activity involves increase of oxidizing substance; hence the left heart is correspondingly stimulated. When, however, adrenal insufficiency occurs, the phenomena follow an opposite course; when total inhibition of the adrenal system exists, the vascular walls, losing all their functional stimuli,—the adrenal secretion, the granules (?), and the oxidizing substances,—gradually cease their contractions and lapse into diastole.

THE INNERVATION OF THE HEART.

We are again brought, by analysis, to the realization that the [illegible] nerves distributed to the heart create and govern functional activity [illegible] according to the destination



MECHANISM OF CARDIAC ACTION. *[Sajous.]*

1, Inferior Vena Cava, the blood of which contains Adrenal Secretion. 2, Hepatic Veins, the blood of which contains granules β derived from the Liver. 3, Right Auricle. 4, One of the Coronary Arteries. 5, One of the Coronary Veins. 6, One of the Foramina Thebesii.

of vital processes *per se.* Indeed, in the heart they do naught else than in other parts of the organism. One set of nerves distributed to the cardiac arteries provokes dilation to increase cardiac activity; another set causes constriction of these vessels when cardiac activity is to be reduced. "The rich nervous supply of the heart is derived from the coronary *plexuses,*" says Piersol, "and *includes* numerous medullated fibers coming from the *pneumogastric* as well as the non-medullated *sympathetic* fibers proceeding from the cervical ganglia. Numerous microscopical ganglia are found along the course of the large nerve-trunks accompanying the branches of the coronary arteries, especially in the longitudinal interventricular and in the auriculo-ventricular furrows. Many additional small groups of ganglion-cells occur within the muscular tissue associated with the fibers supplying the intimate structure." Briefly, according to prevailing teachings the vagus and sympathetic are the nerves which govern the functions of the heart.

Is this true? In the light of my own views, it is subject to doubt; and, precisely as I have shown it to be the case with the kidneys, all the nerves supplied to the heart belong to the sympathetic system.

ACCELERATION.—Legallois, early last century (1812) urged that the nerves which increased the beats of the heart in a given time belonged to the sympathetic system. Although vigorously attacked by Bezold and others, this doctrine has steadily gained ground, and most investigators, including Heidenhain, Langley and Gaskell have accepted Legallois's view. It becomes a question, however,—in the light of my views,—whether acceleration represents the motor phase of cardiac action, and therefore, whether or not as in the kidney, the sympathetic fulfills the rôle of motor, *i.e.*, of vasodilator nerve. That it does is shown by the experiments of E. and M. Cyon[16] who found that occlusion of cardiac vessels did not cause acceleration—in other words that it was not by *reducing* the blood supplied to the heart walls that the accelerators acted upon the heart. On the other hand, as will be shown under the next heading, constriction of the cardiac arteries, *i.e.*, diminution of the blood supplied to the cardiac muscle, slows the heart's action. Indeed, Baxt[17] observed a distinct antagonism between the vagi in the neck—owing as shown below to the presence of cardiac vasoconstrictor fibers in this nerve—and the accelerators, when stimulated simultaneously. The vagi suppressed the accelerators invariably, in fact, and irrespective of the strength of the current. It is evident, therefore, that acceleration is not due to constriction of the cardiac arteries, and that the sympathetic accelerators must act upon the heart by producing dilation of these vessels.

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[16] E. and M. Cyon: Archiv f. Physiol., 1867.

The vasodilator properties of the accelerators have, in fact, so legitimate a claim to recognition that in his recently published review of our knowledge on the subject Carvallo[18] remarks: "The first thoracic ganglion, or stellate ganglion seems to contain vasodilator fibers which almost always cause augmentation of speed." He forcibly illustrates this fact by a table demonstrating that the vessels so influenced show *an increased blood-flow in a given time,* when the accelerator nerves are stimulated, and closes his review with the following words: "We may conclude therefore that the heart possesses a complete vasomotor apparatus the vasoconstrictor fibers of which reach it essentially by way of the vagus, and the vasodilator nerves by the stellate ganglia [first thoracic] and the annuli of Vieussens."

Briefly, "acceleration" represents an exacerbation of activity of the heart, and just as we found such increased activity produced by vasodilation and the admission of an excess of blood, in other organs, so do we find it here.

INHIBITION.—In the light of foregoing statements, this phenomenon should assert itself as a result of excessive constriction of the cardiac arteries and diminution of the blood supplied to the cardiac muscle. That such is the case suggests itself from various directions.

The inhibitory effect of excessive constriction of the coronaries is beyond question. Chirac[19] found that the beats of a dog's heart were soon arrested when one of the coronaries was tied. Erichsen[20] observed a similar result after tying these vessels. Leonard Hill[21] referring to the investigations of Cohnheim and Schulthess-Rechberg,[22] McWilliams,[23] Bettelheim,[24] and others, also states that "ligaturing one of the large branches only is frequently sufficient to cause arrest." Again, Sée, Bochefontaine and Roussy[25] observed that substances capable of plugging the coronaries—lycopodium spores, for instance—also caused cardiac arrest. Porter[26] plugged the left coronary artery in nineteen dogs and says that "the closure of the artery was always promptly followed by arrest." As the result of closure by ligation in sixty-seven dogs, he reached the deduction that "the frequency of arrest is in proportion to the size of the artery ligated." As cardio-inhibitory impulses transmitted through the vasoconstrictors of both vagal trunks probably influence *all* the cardiac arterioles simultaneously, the ease with which the heart's action can be arrested by exciting the bulbar center is easily accounted for. Finally Kolster,[27] Porter,[28] and others have shown experimentally that the part of the heart supplied by an infarcted coronary artery degenerates.

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[17] Baxt: Arb. a. d. phys. Anst., Leipzig, 1875.
[18] Carvallo: Richet's Dictionnaire de Physiol., p. 347,
[19] Chirac: "De Motu Cordis," p. 121, 1698.

Yet, if the vasomotor impulses inhibit the heart by causing excessive constriction of the coronaries and their offshoots, the effects on the heart wall must coincide with those resulting from deprivation of blood. Such is undoubtedly the case: E. Weber[29] observed that during partial inhibition the cardiac contractions were weakened, while Schiff[30] found that the muscular elements of the entire organ responded less or not at all to stimuli. François-Franck, Fischel,[31] and others observed that the cardiac walls were softer than usual. Foster[32] states that when the interrupted current is used to stimulate the vagal trunk, the heart remains in diastole, motionless and flaccid. When, however, the current is weak, the beats are only slowed and weakened. Coats[33] ascertained manometrically that the contractions were markedly reduced in force. Gaskell[34] and Stefani[35] found that the ventricular tonicity was reduced. Muskens[36] also found that stimulation of the vagus lessened the force of the contraction in the frog.

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[20] Erichsen: London Hospital Gazette, vol. ii, p. 561, 1842.

[21] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 1, 1900.

[22] Cohnheim and Schulthess-Rechberg: Virchow's Archiv, Bd. lxxxv, H. 3, S. 503, 1881.

[23] McWilliam: Jour. of Physiol., vol. viii, p. 296, 1887.

[24] Bettelheim: Zeit. f. klin. Med., Bd. xx, S. 436, 1892.

[25] Sée, Bochefontaine and Roussy: C. R. de l'Acad. des sci., T. xcii, p. 86, 1881.

[26] Porter: Jour. of Exper. Med., vol. i, p. 46, 1896.

[27] Kolster: Skandinav. Archiv f. Physiol., Bd. iv, p. 1, 1893.

[28] Porter: Pflüger's Archiv, Bd. lv, Hft. 7 u. 8, S. 366, 1894.

[29] E. Weber: "Handwörterbuch d. Physiol., Bd. ii, S. 42, 1846.

[30] Schiff: Archiv f. Physiol. Heilk., 9ter Jahrgang, S. 22, 1850-51.

[31] Fischel: Archiv f. exp. Path. u. Pharm., Bd. xxxviii, Hft. 3 u. 4, S. 228, 1897.

[32] Foster: "T. B. of Physiol.," sixth American edition, Phila., 1895.

Gaskell[37] characterizes as "most striking" the attending *depression of activity.* Still, there is no loss of inherent muscular irritability, since, according to Foster,[38] a pin prick in the heart during inhibition may cause the organ to resume its beats; the morbid phenomena are, therefore, the result of a deficient supply of the nutrient components of the blood. Porter[39] states that "but little is known as to the constituents of the blood which are essential to the life of the mammalian heart," and that "an abundant supply of oxygen is certainly highly important." The manner in which the deficiency of these blood constituents causes the inhibitory effects is suggested in the following lines of Langley's[40]: "The decrease of rigidity in the inhibited muscular tissue shows that inhibition is not caused by the development of a contractile force acting in a direction opposed to the normal one and overpowering it. We are then brought to the conclusion that certain nerve impulses —the inhibitory nerve impulses—are able to *lessen* or to *stop* the chemical change *in the tissue* which leads to contraction."

The rôle of the "inhibitory" fibers (now generally considered as vagal, because they form part of the nerve bundles which have been known as the vagi, or pneumogastric nerves) thus corresponds with that of the sympathetic vasoconstrictors we have found, elsewhere, to restore the arterioles to their normal caliber after these vessels had been dilated by a motor or secreto-motor nerve to incite an exacerbation of functional activity. Langley's observation gives precision to my view in this connection; interpreted from my standpoint, it is the diminution of blood in the cellular elements which serves "to lessen or to stop the chemical change in the tissue which leads to contraction." Can we logically, in view of the secreto-motor rôle ascribed by physiologists to the vagus in other organs, admit that in the heart its action is the opposite? That the so-called "inhibitory" nerve is composed of sympathetic fibers which carry on the same functions they do in other organs, is therefore evident.

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[33] Coats: Bericht d. k. Sachs. Gesellsch. d. Wissensch., S. 360, 1869.
[34] Gaskell: Philosoph. Trans., p. 1019, 1882.
[35] Stefani: Archives italiennes de biologie, T. xxiii, p. 172, 1895.
[36] Muskens: Pflüger's Archiv, Bd. lxvi, Hft. 5 u. 6, S. 328, 1897.
[37] Gaskell: Schäfer's "T. B. of Physiol.," vol. ii, p. 169, 1900.
[38] Foster: "T. B. of Physiol.," sixth American edition, 1895.
[39] Porter: "Amer. T. B. of Physiol.," vol. i, second edition, p. 148, 1900.
[40] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 616, 1900.

Should we under these conditions consider the sympathetic as "inhibitory"? I have shown that inhibition is the result of excessive constriction of the arterioles. "Excessive" here obviously portrays a morbid or pathological condition, one of grave importance clinically. Indeed, as I will show in the second volume, many toxins and toxics are fatal owing to their vasoconstrictor influence on the cardiac vessels, and the morbid phenomena awakened are precisely those described above—those which the physiologist deems normal because they are expressions of a so-called physiological function he has termed "inhibition."

In my opinion the older term "moderator nerve" should replace the pernicious term now used, and "inhibition" be reserved for the expression of the morbid process which excessive constriction of the arterioles represents.

AUGMENTATION.—This action of the heart, *i.e.*, increase of its contractile power, must be due to an action other than that of acclerator nerves. Thus, von Bezold and Bever[41] and later Cyon[42] found that stimulation of the accelerator increased the number of beats of the heart, but not its power. This was confirmed by other investigators. Again the mode of action of the augmentor nerve differs strikingly from that of other cardiac nerves; Foster,[43] for instance, writes: "In contrast with the case of the vagus fibers, a somewhat strong stimulation is required to produce an effect; the time required for the maximum effect to be produced is also remarkably long." These facts suggest that acceleration and augmentation are separate functions. Indeed, the delay in the augmentation of power, as compared with the acceleration, is explained when, as I urged a few years ago,[44] the adrenal secretion is regarded as the source of the increased cardiac power. This is sustained by many facts. Thus, while Noel Paton[45] refers to the "augmentors and accelerators" as small medullated, *i.e.*, sympathetic, fibers "which leave the spinal cord by the anterior roots of the second, third, and fourth dorsal nerves passing to the stellate ganglion," I have shown that the three above-mentioned roots are also precisely those through which the nerves which pass to the sympathetic chain and thence down to the splanchnic, to finally reach the adrenals. On stimulating these nerves, therefore, an experimenter not only excites the accelerators which pass to the heart via the annulus of Vieussens, but also the nerve-paths to the adrenals.

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[41] Bezold and Bevér: Untersuch. a. d. physiol. Lab. zu Wurzburg, Bd. ii, 1867.

[42] Cyon: *Loc. cit.*

[43] Foster: *Loc. cit.*, p. 203.

This accounts for the fact that while a large group of investigators including Cyon, Bezold, Schmiedeberg, Boehm and Bowditch observed acceleration without increase of power, others, equally competent, including Heidenhain, Mills, Roy and Adami, and Bayliss and Starling observed both phenomena. Indeed Schmiedeberg and Bowditch both urged the presence of two different sets of nerves to account for these specific effects, the one set influencing the cardiac beats, the other "acting upon the blood-pressure without influencing frequency." Now, the marked influence of the adrenal secretion upon the blood-pressure is well-known, and the delay in the appearance of "augmentation" is explained when it is borne in mind that the activity of secretory organs had to be awakened before the "augmentation" and the rise of blood-pressure could become manifest. Biedl,[46] in fact, found that stimulation of the divided splanchnic only caused an increased production of adrenal secretion after 7 to 9 seconds.

I submitted in the two preceding sections, the reasons which had led me to conclude that the adrenal secretion contributed to the contractile power of the right ventricle which it reaches with the venous blood of the inferior vena cava. Now, Brown-Séquard[47] had many years earlier (1853) urged the predominating influence of the blood of this vein upon cardiac dynamism, a view sustained by Radcliffe (1855); but Castell having found that a frog's heart when detached failed to beat with increased vigor in carbonic acid gas, and overlooking the fact that some other substance in the venous blood might have acted on the heart, physiologists disregarded Brown-Séquard's observation. Additional evidence to this effect is submitted in the second volume.

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[44] Sajous: Jour. Amer. Med. Assoc., Feb. 4, 1905.

[45] Noel Paton: "Essential of Human Physiol.," p. 243, 1905.

[46] Biedl: *Loc. cit.*

The presence of "augmentor" and "pressor" fibers in the sympathetic splanchnic accounts for the fact long ago recorded by von Bezold and Bensen,[48] that section of both splanchnics lowered the blood-pressure as much as section of the spinal cord in the cervical region, while Strehl and Weiss found that, after removing one adrenal, the blood-pressure could be lowered by clamping the suprarenal vein of the remaining organ, thus depriving the blood of any adrenal secretion, and that by releasing this vein the blood-pressure was soon restored to its previous level. As I view the process, however, excitation of the lower segment of the upper sympathetic cord after dividing it should raise the blood-pressure. Bezold found that this procedure raised the blood-pressure as much as *seven times* its initial level; Ludwig and Thiry showed, moreover, that the same result could be obtained after severing all the nerves to the heart.

Augmentor effects attended by a rise of the blood-pressure may also be produced through the intermediary of another organ. Cyon and Aladoff[49] found that stimulation of the annulus of Vieussens (which also contains pure accelerator fibers) raised the blood-pressure. Cyon had already found in 1867 that when the cervical sympathetic was divided on a level with the inferior cervical ganglion, and its *upper* segment was excited the strength of the heart-beats was markedly increased.

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[47] Brown-Séquard: Exper. Researches applied to Phys. and Path., N. Y., London, and Paris, 1853.

[48] Von Bezold and Bensen: Neue Würzberger Zeitung, 1866; Verh. d. Phys. med. Gesells., Würzburg, January, 1867.

[49] Cyon and Aladoff: Bull. de l'Acad. des Sci. de St. Petersburg, vol. vii, 1871.

A recent study of the question (1898)[59] by the same physiologist showed that these "reënforced pulsations" which he had at first ascribed to reflex action, were in reality due to the fact that the nerves which evoke these phenomena were distributed to the vessels of the thyroid gland and that it was the secretion of this organ which had produced the cardiac "augmentation." The manner in which the thyroid secretion could produce this effect is readily explained by the fact that, as I have shown, this secretion serves to sustain the functional efficiency of the adrenal center. Briefly, it is also through the adrenals—though indirectly—that Cyon produced "reënforced pulsations" of the heart.

The following conclusions seem to me, in the light of the foregoing facts, to summarize the functional mechanism of the heart:—

1. The nervous supply of the heart is derived from the sympathetic system and is composed of two sets of nerves: the accelerator and the moderator (or inhibitory) nerves.

2. The accelerator nerves increase the rapidity of the contractions of the heart, by causing dilation of its arterioles and thus increasing the volume of blood admitted to its muscular elements.

3. The moderator (or inhibitory) nerves diminish the rapidity of the heart's contractions, by causing constriction of its arterioles and thus reducing the volume of blood admitted to its muscular elements.

4. "Augmentation," i.e., *increased power of the heart's contractions is due to increased activity of the adrenals, whose secretion traverses the heart on its way to the lungs.*

As to the physico-chemical process involved—bearing in mind that the muscular elements are inherently contractile—they are, pending additional data, as follows:—

5. The mechanical energy upon which the right heart depends is of two kinds: (1) the contractile action of the adrenal secretion brought to it by the inferior vena cava; (2) the continuous action of the oxidizing substance of the coronary arterial blood upon myosinogen formed from granules β, the latter being granulations derived from leucocytes.

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[59] Cyon: Arch. de physiol. norm. et path., vol. x, No. 5, p. 618, 1898.

6. The adrenal secretion and the granulations β enter the right auricle and the right ventricle with the blood of the vena cava.

7. The adrenal secretion, owing to its direct action on muscular tissue, causes the walls of these cavities to contract alternately upon their venous contents and to force a small quantity of the latter into the Thebesian foramen and channels.

8. This blood then penetrates the interfibrillary spaces of Henle,—i.e., *around the bare muscle-cells,—and its granules β are used by the latter to build up their myosinogen.*

9. As the plasma of the coronary arteries and their terminals, the pericellular capillaries of the muscle-elements, contains oxidizing substance (adrenoxidase) contraction of the muscle-cells is induced as it is elsewhere in the organism.

10. The adrenal secretion and the granules β, which do not enter the Thebesian channeds, are carried to the lungs with the venous blood of the right ventricle.

11. The mechanical energy of the left heart is supplied (1) by the oxidizing substance of the arterial blood, which penetrates its muscular structures and its cavities by the coronaries and the pulmonary veins, and (2) by an additional supply of granulations β, and perhaps of adrenal secretion, which find their way to its myocardium through the Thebesian channels that connect it with the right heart.

12. The manner in which the contractile process is carried on in the walls of the left heart is similar to that which prevails in the right heart.

THE ADRENAL SECRETION IN ITS RELATIONS TO RESPIRATORY FUNCTIONS.

The rôle of the adrenal secretion in respiration, and particularly the process through which oxygen is taken up by the blood, was reviewed in the second chapter. I believe that the succeeding chapters, by affirming the importance of the oxidizing substance in every part of the organism, have but confirmed the conclusions reached concerning the process in question. The fact that the interchange of oxygen and carbonic acid between the alveolar air and the blood by mere diffusion was inadequate to account for the experimental results of various investigators, particularly Bohr and Haldane and Smith, has therefore been correspondingly emphasized. I must also refer to the fact, however, that the belief of Ludwig, Bohr, and others, that the alveolar tissues might be the seat of functions capable of fulfilling the missing requirements of the process, has not been sustained by my inquiry. On the other hand, the rôle of the adrenal secretion in the lungs as I have defined it has adequately met these requirements, notwithstanding the severe tests to which it has been submitted in previous chapters.

We have seen that the adrenal secretion, conveyed to the lungs with the venous blood, is not only able to take up oxygen, but to form an oxidizing substance, *i.e.*, adrenoxidase, with which hæmoglobin can, in the lungs, become replenished with oxygen. The entire set of analyses submitted in this work so far, however, has served further to emphasize another fact: *i.e.*, that *the plasma, and not the corpuscle, is the dispenser of oxygen*, the corpuscle being a mere carrier from which the plasma itself becomes replenished as needed. As already stated, this precisely coincides with the conclusion to which Jaquet was led by chemical methods after Salkowski (1881) had obtained oxidations from blood alone, which he attributed, however, to the blood-corpuscles. Abelous and Biarnès having obtained oxidation of salicylic aldehyde by means of blood-*serum*, Salkowski modified his former view and experimentally confirmed the results of the other investigators.

Finally, we have seen how closely connected the adrenal secretion is with the integrity of the blood, and how readily the hæmoglobin molecule becomes dissociated in proportion as the efficiency of the adrenals becomes weakened.

The next important question to analyze is one fraught with considerable confusion, viz., the manner in which the respiratory process is governed, and the identity of the respiratory center.

THE NERVO-VASCULAR MECHANISM OF THE LUNGS.

According to prevailing teachings the respiratory center is located in the medulla oblongata, *i.e.*, the bulb. But there is considerable evidence on record indicating that the bulbar center is not supreme in the control of respiration, although the fact that it forms part of the controlling mechanism cannot be denied. Thus, division of the cord below the seventh cervical nerve arrests costal respiration; section below the medulla causes all thoracic movements to cease; removal of the brain *above* the medulla, the seat of the supposed center, does not stop respiration, while cessation of this function occurs when the medulla is removed or extensively injured, save in exceptional cases. After reviewing this evidence Professor Foster adds: "Nay, more; if only a small portion of the medulla—a tract whose limits have *not been clearly defined*,[51] but which may be described as lying below the vasomotor center in the immediate neighborhood of the nuclei of the vagus nerves—be removed or injured, respiration ceases, and death at once ensues. Hence this portion of the nervous system was called by Flourens the vital knot, or ganglion of life: *nœud vital*. We shall speak of it as the *respiratory center*."

Yet, how account for the facts recited in the following quotation from Noel Paton's text[52]: "Both parts of the respiratory center are under the control of higher nerve centers, and through these they may be thrown into action at any time, or even prevented from acting for the space of a minute or so. But, after the lapse of this period, the respiratory mechanism proceeds to act in spite of the most powerful attempts to prevent it.

"To determine its mode of action the influence of afferent nerves upon the center must be considered.

"*Vagus.*—Since the vagus is the nerve of the respiratory tract we should expect it to have an important influence on the center.

"*Section of one vagus* causes the respiration to become slower and deeper; but, after a time, the effect wears off, and the previous rate and depth of respiration is regained.

"*Section of both vagi* causes a very marked slowing and deepening of the respiration, which persists for some time, and passes off slowly and incompletely. Now, if after the vagi have been cut, the connection of the center with the *upper brain*

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[51] The italics are mine.

[52] Noel Paton: *Loc. cit.*, p. 291.

tracts is severed, the mode of action of the center totally changes. Instead of discharging rhythmically it remains for a long period at rest, then the inspiratory center discharges violently, causing a strong and prolonged contraction of the muscles of inspiration. This passes off, and again a period of rest of variable duration sets in, to be again interrupted by another more or less long and strong discharge.

"Separation of the respiratory center from the vagi and upper brain tracts brings about a loss of its rhythmic action, *but does not stop its activity*. The center owes the rhythmic nature of its action to afferent impulses. These afferent impulses reach it normally through the vagi, but when these are cut the upper brain takes upon itself the function of maintaining the rhythm."

Howell[53] also says, referring to the "midbrain, at the level of the posterior colliculi" (the corpora quadrigemina) a region above the medulla oblongata: "Martin and Booker[54] found that stimulations in this region caused a marked increase in the rate of inspiratory movements and finally a standstill in inspiration—that is, a complete tetanic contraction of the inspiratory muscles lasting during the stimulation. Lewandowsky[55] has shown that section of the brain stem at or below the inferior colliculi causes an alteration in the respiratory rhythm similar to that following section of both vagi. After cutting through the inferior colliculi further sections more posteriorly do not add to the effect. He considers that there is an automatic inhibitory center in the midbrain which influences continually the automatic activity of the medullary center." Again, Ott[56] writes: "I have made numerous experiments to determine the exact seat of the polypnœic center. To establish a center three things are necessary: (1) that its abolition causes the phenomena to disappear; (2) that irritation—mechanical, chemical or electrical—causes the phenomena to be present, and (3) that the part of the nervous system exhibiting these peculiarities be circumscribed in extent. After numerous observations and experiments it was found that pressure upon the tuber cinereum with a pledget of cotton, or even slight puncture, increased the normal respirations to the point of polypnœa. Complete puncture in a normal animal was followed by a rise to 106° F. within two hours, even though the animal was bound down and had been subjected to considerable shock.

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[53] Howell: "T. B. of Physiol.," second edition, p. 640, 1907.
[54] Martin and Booker: Jour. of Physiol., 1, 370, 1878.
[55] Lewandowsky: Archiv f. Physiol., 489, 1896.
[56] Ott: "T. B. of Physiol.," second edition, p. 451, 1907.

"If now the animal whose tuber is punctured be heated, there will result *no* polypnœa, even though a temperature of 107° F. be reached. I am convinced that the *tuber cinereum is a center of polypnœa and thermotaxis.*"

A suggestive feature asserts itself in this connection: As I have pointed out, and as will be further shown in the second volume the tuber cinereum is precisely the region through which the nerve path from the pituitary body to the adrenals passes to the medulla oblongata, and thence, via the spinal cord and the sympathetic nerves and ganglia, to the adrenals, whose secretion, we have seen, serves to take up the oxygen of the air and to distribute it to the tissues, *i.e.*, to sustain oxygenation. Moreover, as emphasized by considerable evidence submitted in the second volume, the walls and floor (of which the tuber cinereum forms part) of the third ventricle, are the pathways of a vast array of sympathetic fibers which likewise pass from the posterior or neural lobe of the pituitary (via the nucleus magnus grisei) to the medulla and cord and thence to be distributed through the sympathetic chain and its offshoots to all parts of the body including the lungs. We have here the explanation of the presence of so-called heat and respiratory centers in this region, *i.e.*, irritation phenomena following the experimental lesions in the course of these nerve-paths,—a fact further sustained by the observation of many experimenters that removal of the pituitary body—the seat of the heat and main respiratory centers in the light of my views—is followed by marked lowering of the temperature and dyspnœa.

How does the respiratory center—or centers, for as stated, the bulbar center is endowed with important functions—influence the respiratory mechanism? Before this feature of the subject can be analyzed, a brief review of the circulation and innervation of the lungs may prove advantageous.

The pulmonary circulation as regards vascular distribution is succinctly portrayed in the following description by Miller,[57] as given by Böhm and von Davidoff[58]: "The *pulmonary artery* follows closely the bronchi through their entire length. An arterial branch enters each lobule of the lung at its apex, in close proximity to the bronchus. After entering the lobule the artery divides quite abruptly, a branch going to each infundibulum; from these branches the small *arterioles* arise which supply the alveoli of the lung. 'On reaching the air-sac the artery breaks up into small radicles, which pass to the central side of the sac in the sulci *between* the air-cells, and are finally lost in the rich system of capillaries to which they give rise. This net-work surrounds the whole air-sac and communicates freely with that of the surrounding sacs.' This capillary net-work is exceedingly fine, and is shrunken *into* the epithelium of the air-sacs; so that between the epithelium and the capillary there is only the *extremely delicate* basement membrane. The infundibula, the alveolar ducts and their alveoli, and the alveoli of the respiratory bronchioles are supplied with similar *capillary net-works.* The veins collecting the blood from the lobules lie at the periphery of the lobules in the interlobular connective tissue, and are as far distant from the intralobular arteries as possible. These veins unite to form the larger pulmonary veins. The bronchi, both large and small, as well as the bronchioles, derive their blood-supply from the *bronchial arteries,* which also partly supply the lung itself. Capillaries derived from these arteries surround the bronchial system, their caliber varying according to the structure they supply: finer and more closely arranged in the mucous membrane, and coarser in the connective-tissue walls. In the neighborhood of the terminal bronchial tubes the capillary nets anastomose freely with those of the *respiratory* capillary system." To avoid confusion I may recall the fact that, while the *pulmonary* artery and its branches contain *venous* blood, and the *bronchial arteries* and their branches carry *arterial* blood, the pulmonary *veins,* on the contrary, contain *arterial* blood. When, therefore, bronchial capillaries are said to empty into the pulmonary veins, it is not used, or venous, blood that is transferred to the latter, but arterial blood originally derived from the thoracic aorta or its primary branches.

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[57] Miller: Journal of Morphology, vol. viii, p. 165, 1893.

[58] Böhm and von Davidoff: *Loc. cit.*

The lungs, as is well known, are innervated by the vagus and the sympathetic system. These unite to form plexuses, the anterior and posterior, which enter the organs with the bronchial tubes and accompany them along their ramifications. The anterior pulmonary plexus, made up of vagal and sympathetic filaments, overlies the pulmonary artery, while the richer posterior pulmonary plexus, composed also of vagal filaments, intermixed with sympathetic fibers from the second, third, and fourth thoracic ganglia, follows the bronchi to their ultimate subdivisions.

According to prevailing views, the vagus—both its sensory and motor fibers—is alone regarded as the intermediary between the respiratory center and the organs of respiration, but as shown in the second volume, the neural lobe of the pituitary also contains the sympathetic center. This proximity to the respiratory center and the important rôle the sympathetic plays in respiration pointedly suggest that both centers are functionally united.

Indeed, there is good ground for the belief that the experimental phenomena now ascribed to the vagus are partly of sympathetic origin—sympathetic in the sense that they are essentially vasoconstrictor as in other organs previously reviewed. Sappey, for instance, writes[59]: "Section of both pneumogastrics in the median portion of the neck not only abolishes the sensibility of the respiratory mucous membrane and paralyzes the internal respiratory muscles; it also involves as consequence a mucous *effusion* into the bronchi, *engorgement* of the lungs, emphysema of these organs, and a very sensible diminution in the number of inspirations." We have in the pulmonary engorgement an evident result of variation of vascular caliber, and inasmuch as we are dealing with a *division* of the nerve, the effect on the vessel must have been one of relaxation. On the other hand, we have in the paralysis of the internal respiratory muscles evidence that a motor nerve—

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[59] Sappey: "Traité d'Anatomie Descriptive," vol. III, p. 397.

a vasodilator, or stricto-dilator, in our sense—was also severed. These dual phenomena indicate that the vagus, as we have seen in the case of the heart, must have contained vasoconstrictor, *i.e.*, sympathetic fibers.

The presence of vasoconstrictor fibers is, in fact, generally recognized. François-Franck, in 1881, showed that the sympathetic nerves distributed to the lungs, caused vasoconstriction, these fibers being stimulated at the entrance into the lungs. Bradford and Dean[60] also demonstrated the presence of vasomotor nerves in these organs after a series of exhaustive experiments. In a subsequent study of the subject François-Franck[61] noted the paradoxical fact that vasoconstriction of the pulmonary vessels caused the lungs to swell, instead of being reduced in volume. This is readily accounted for when it is recalled that the vasoconstriction applies only, in the light of my views, to the arterioles. These small pre-capillary vessels being constricted, the arterial blood was dammed up behind the seat of obstruction in François-Franck's experiment, thus causing the larger portions of the vessel, which are not governed by the sympathetic, to dilate.

A source of confusion asserts itself in this connection, however, which we have also encountered while studying the heart. The experiments of Rose Bradford and Dean[62] are thus referred to by François-Franck: "They carefully sought the points of emergence, from the cord, of the filaments which cause elevation of pulmonary pressure and lowering of aortic pressure: that is to say, pulmonary vasoconstriction. These were located from the second to sixth dorsal, and, in respect to maximum effects, on a level with the third, fourth, and fifth nerves. The pulmonary vasoconstrictors ascend the chain up to the first thoracic ganglion, where they become detached, to reach the pulmonary plexuses." The salient feature of the topography of these nerves is that the lower limit of the ganglionic chain through which they pass happens to be the upper limit of the ganglia from which the splanchnic nerves that ultimately carry impulses to the adrenals are given off. While the pulmonary vasoconstrictors which pass directly to the lungs from the first thoracic to the pulmonary plexuses are, as generally taught, true vasoconstrictors, the presence in the second, third, and fourth ganglia of the sympathetic chain, of the nerves to the adrenals suggests that many vasoconstrictor phenomena attributed to the direct action of nerves, should be ascribed to an increase of adrenal secretion in the blood. Indeed Jacobi[63] found that intense vasoconstriction of the intestinal vessels (inhibition) produced by excitation of the splanchnic was replaced by ordinary vasoconstriction after the suprarenal nerves had been cut.

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[60] Bradford and Dean: Jour. of Physiol., vol. xvi, p. 34, 1894.
[61] François-Franck: Arch. de Physiol., T. viii, p. 184, 1896.
[62] Rose, Bradford and Dean: Journal of Physiol., p. 57, 1894.

The fact, moreover, that the introduction of adrenal extract into the circulation produces general vasoconstriction is well known. Mankowsky,[64] for example, noted "a great increase in blood-pressure and stimulation of the cardiac and respiratory centers." This occurred "even when the animals (dogs) were under the influence of chloroform, morphine, or chloral hydrate." "In cats, says Swale Vincent,[65] "by far the most noticeable feature was an enormous rapidity of the respiratory movements in the early stage." The two—now familiar—stages that occur under the influence of toxic doses of suprarenal extract, as well as under that of other poisons, are well illustrated in the following observation by the same investigator: "In the early stage of poisoning respiration is quick and shallow and the heart is excited. Subsequently the breathing and heart-beats become feeble, and finally the respiration is deep and infrequent." Finally, the fact that all these phenomena are independent of the cord has been shown by Biedl,[66] who, as we have seen, obtained marked increase of blood-pressure after injections of suprarenal extract, notwithstanding the fact that all the spinal structures had been removed.

This does not mean that the adrenal secretion fulfills any particular function in the lungs other than that of taking up oxygen therein; it is only intended to show that excitation of the splanchnic nerve may suggest the presence of pulmonary vasoconstrictor nerves in this great nerve-path, when the vasoconstrictor effects witnessed in the lungs are in reality due to the presence in the blood, as a result of splanchnic stimulation, of an excess of adrenal secretion.

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[63] Jacobi: Archiv f. exper. Path. u. Pharm., vol. xxix, p. 171, 1892.
[64] Mankowsky: Russian Archives of Pathology, etc., Mar, 1898.
[65] Swale Vincent: Jour. of Physiol., Feb. 17, 1898.
[66] Biedl: Wiener klin. Wochen., ix, 1896.

As to the rôle of the vagus in the respiratory organs, our views differ from those at present taught only in that they explain, as was the case with other organs, *how* the physiological phenomena are produced.

I have briefly referred to the manner in which the vagal fibers are distributed in the lungs. Sappey[67] also studied the distribution of vagal nerves in the lungs of mammals, including particularly those of man, the ox, and horse, and reached the following conclusions: "1. They follow the subdivisions of the air-tree to their terminal extremities; they do not leave these subdivisions and follow them to the lobules. 2. All those that leave the anterior pulmonary plexus and the much greater number given off by the posterior pulmonary plexus preserve their plexiform arrangement throughout their entire distribution; their meshes are elongated only in the line of their axis, each thus constituting an elongated ellipse. 3. Their ramifications, essentially destined for the muscular coat of the bronchi and respiratory mucous membrane, have no connection with the blood-vessels." Berdal, on the other hand, confirms this, and indicates the rôle of the sympathetic terminals in the following lines: "The branches of the penumogastric are destined for the bronchi; the branches of the great sympathetic are lost in the walls of the arteries."

The statement of Sappey that the vagal ramifications of the vagus have no connection with the blood-vessels, introduces a feature of importance which applies to all other organs reviewed, viz.: that besides the vasodilator and vasoconstrictor nerves which govern the function of any organ, there are sensory terminals which, as such, transmit afferent impulses to the centers (primary or subsidiary) which govern the local blood supply. Indeed, we have seen that section of the vagi in the neck caused loss of sensation in the respiratory mucous membrane, paralyzed the bronchial muscles, and gave rise to effusion of mucus into the bronchi and engorgement of the lungs. How can all these phenomena be accounted for without granting sensory as well as motor and vasomotor functions to the vagal supply? Loss of sensation points to inhibited function, and not to engorgement of the bronchial mucous membrane. And yet we may have engorgement without functional erethism, if it is due, not to the presence of blood fully charged with oxygen, but to blood which, through the very fact of being dammed up in the vascular channels, is reduced therein to practically the condition of venous blood. The effusion of mucus into the bronchi and pulmonary engorgement would occur as normal consequences of such a state of things. But how account for this vascular dilation without granting such attributes to the vagal plexuses?

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[67] Sappey: *Loc. cit.*, p. 391.

Again, the fact that cutting of both nerves in the neck gave rise to paralysis of these muscles points to another suggestive feature, namely: that the vagus must *incite* and *govern* the motor impulses to these muscles, besides presiding over the functional variations of caliber of their vessels. If we now add to these manifestations of *efferent* nervous activity those of *afferent* activity suggested by the loss of sensation over the bronchial mucous membrane, it seems clear that *we have in the vagal nerves referred to an autonomous supply especially devoted to the function of the bronchial tubes and their ramifications down to* — but not including — *the pulmonary lobule.* The importance of this fact asserts itself when we realize that it accounts for the complete isolation of bronchial affections from those of the parenchyma, and gives us a clue to their original cause.

My opinion that the vagus—as motor nerve—acts in the lungs as elsewhere, *i.e.*, as stricto-dilator nerve, is sustained by experimental evidence. As Noel Paton writes[68]: "Strong stimulation of the pulmonary branches of one vagus (below the origin of the superior laryngeal) causes the respiration to become more and more rapid, the inspiratory phase being chiefly accentuated. If the stimulus is very strong respirations are stopped in the phase of inspiration. Weak stimuli, on the other hand, may cause inhibition of inspiration.

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[68] **Noel Paton:** ***Loc. cit.*****, p. 292.**

"Such experiments prove that impulses are constantly traveling from the lungs to the center whereby the rhythmic activity of the center is maintained.

"How do these impulses originate in the lungs? Apparently from their alternate expansion and contraction.

"If the lungs be forcibly inflated—*e.g.*, with a bellows—the inspiration becomes feebler and feebler and finally stops. The nature of the gas, if non-irritant, with which this inflation is carried out is of no consequence. If, on the other hand, the lungs be collapsed by sucking air out of them, the inspiration becomes more and more powerful, and may end in a spasm of the inspiratory muscles.

"This shows that with each expiration a stimulus passes up the vagus which acts upon the inspiratory center to make it discharge. The vagus is thus *a true excito-motor nerve*, making the center act in a reflex manner. With each collapse of the lung the vagus is thrown into action, as the lungs expand it ceases to act, and, as a result, the inspiratory center stops acting, the muscles of inspiration cease to contract, and expiration occurs.

"While ordinary respiration may thus be considered as a rhythmic reflex act, it must not be forgotten that the respiratory center can and does act rhythmically under the influence of the higher center, or a-rhythmically and spasmodically when these as well as the vagi are severed from it."

The mode of action of the vagus as a "true excito-motor nerve" is thus subject in a great measure to the respiratory centers—the main one of which, in the light of my views is located in the neural lobe of the pituitary body. The vagal sensory terminals of the bronchi transmit sensory impulses to this center and excito-motor impulses are transmitted by it to the entire respiratory apparatus, including the thoracic respiratory muscles. The manner in which all these muscles are excited to increased activity by the efferent or excito-motor vagal fibers does not differ from that of all organs reviewed: an excess of blood is admitted into the contractile elements, through dilation of its arterioles. An excess of blood-plasma laden with oxidizing substance is admitted, as previously shown, to the myosinogen of the muscular elements, where inspiration is in order; hence the fact that strong excitation of the vagus "causes the respiration to become," as Paton says, "more and more rapid, the inspiratory phase being chiefly accentuated." When—physiologically—excessive inspiration is to cease, the sympathetic vasoconstrictors come into play: they restore the muscular arterioles to their normal caliber; less blood is admitted to the muscular elements and the inspirations resume their normal rhythm.

But a third factor must now be taken into account: that represented by the functions of the adrenals. And from the standpoint of the clinician, this factor is by far the most important of all the physiological phenomena of the function of respiration. Indeed as will be shown in the second volume, dyspnœa is often the result of adrenal insufficiency, the adrenal secretion produced being inadequate to sustain the oxygenation of the body at large. Again, Miller, we have seen, refers to the subdivision of the pulmonary artery "which divides quite abruptly, a branch going to each infundibulum"; from the latter "small *arterioles* arise which supply the alveoli," while these on reaching the air-sac are said to culminate in "the rich system of capillaries to which they give rise." If the "small arterioles which supply the alveoli" are abnormally dilated through some general dyscrasia and the stream of venous blood of oxygenation of the adrenal secretion it contains is thus imperfectly exposed to the air, we have a logical explanation of the well known beneficial action of belladonna—a sympathetic stimulant which, as we will see, causes constriction of the arterioles, and of potassium iodide, a powerful adrenal stimulant.

That fluctuations in the secretory activity of the adrenals may provoke dyspnœa is well illustrated by the effects of all drugs that are sufficiently active to markedly affect adrenal functions. The action of venoms even more strikingly shows the morbid connection that exists between variations of suprarenal activity and pulmonary functions, even the stage of blood-disintegration being sometimes reached. Noé,[69] for instance, refers to the many observers who have reported intense respiratory phenomena after cobra-bites. Viper-venom was also found by Phisalix to produce at first "accelerated respiration," then "somnolence, with slowing of respiration." Bee-venom in sufficient quantity gives rise to dyspnœa, according to Paul Bert, *black blood* being found in the vessels. Toad-, salamander-, scorpion-, and eel- venoms were found to affect respiration in a similar manner. Mosso noted that the process of death varied with the dose: medium doses first arrest respiration, then the heart; stronger doses arrest both simultaneously. Paralysis of the motor end-plates had evidently nothing to do with this process, since Mosso found the thoracic nerves responsive to the induced current.

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[69] Noé: *Loc. cit.*

Removal of the adrenals under these conditions should give rise to phenomena similar to a violent dose of venom. Cybulski not only observed,[70] under such conditions, marked dyspnœa, a fall of the vascular pressure to zero, and hæmoglobinuria, but also found that the injection into the veins of an aqueous 10-per-cent. solution of suprarenal extract "immediately caused these phenomena to disappear." Boinet[71] states that after removal of both organs in a large number of rats the respiration became "slow, painful, and difficult." Briefly, the functions of the adrenals are as important features of the respiratory function as any of those generally recognized. It is now possible to understand why the nerve paths of the heat and respiratory centers are so intimately related in the third ventricle. Originating from a common center, the pituitary body, the vagal, sympathetic and adrenal nerves, jointly project from their common source, the pituitary body, to reach, by way of the tuber cinereum, the walls of the third ventricle and the midbrain, the medulla oblongata, where they form subsidiary (and probably coördinating) centers whence the impulses to the respiratory organs are transmitted.

The newer features of the nervo-vascular mechanism of (ordinary tranquil) respiration which I submit in the foregoing pages, pending additional evidence and detail, may be summarized as follows:—

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[70] Cybulski: Gazeta Lekarska, March 23, 1895.
[71] Boinet: *Loc. cit.*

1. The bulbar respiratory center is not, as now believed, the sole, or even the most important, center of this class; it is a subsidiary and, probably, a co-ordinating center.

2. The primary and chief respiratory center is located in the pituitary body and consists of three functionally related centers, the adrenal, vagal, and sympathetic centers, which, in turn, are connected by nerve-chains with the corresponding subsidiary centers in the bulb, and govern, through the intermediary of the latter, the respiratory mechanism.

The chief respiratory center carries on its functions as follows:—

Its adrenal center, by governing the production of the adrenal secretion, which takes up the oxygen of the air and forms the albuminous constituent (96 per cent.) of hæmoglobin, regulates the proportion of this oxidizing substance (the adrenoxidase) supplied to the blood.

Its vagal center, acting through the vagus (the intercostals and phrenic) as excito-motor (stricto-dilator) nerves of inspiration, provokes contraction of the muscles which dilate the larynx, the bronchi, and the thorax and depress the diaphragm, and thus increase the intake of air by the lungs, i.e., *the supply of oxygen from which the adrenal secretion and the hæmoglobin absorb oxygen to distribute it to the tissues.*

Its sympathetic center, acting, through the sympathetic nervous system, as antagonist of the vagal center to provoke expiration, causes all the above-mentioned respiratory muscles to relax passively (by constricting their arterioles), thus enabling the larynx and bronchi to resume their normal caliber, the thorax to contract, and the diaphragm to rise, in order to insure the expulsion of the expiratory air laden with carbonic acid.

THE ADRENAL SYSTEM AND THE KIDNEYS.

The belief that the kidneys are the source of an internal secretion dates back to 1869, when Brown-Séquard showed that injections of renal extract postponed the development of uremia in nephrectomized animals, and prolonged life. Lépine found in addition that a filtrate of a watery extract of kidney caused a rise of temperature and dyspnea. Moreover, Oliver and Schäfer showed in 1898 that a cold-water extract of fresh kidney, when injected intravenously in rabbits, soon produced a more or less marked rise of the blood-pressure. This observation has been sustained by Bingel and Strauss,[72] who isolated the pressor substance and called it "rennin." Conversely, Pearce[73] found that extracts of the kidneys of dogs with experimental uranium and chromium nephritis, prepared at a time when the urine is free of the normally present depressor substance, have no pressor effect. Pearce holds that it is thereby conclusively shown that the dog's kidney does not contain a pressor substance. Yet, so many observers have confirmed the results of Oliver and Schäfer that for the time being, at least, the presence of a pressor substance in the kidney must be regarded as at least probable.

In the light of the data I have adduced, however, none of the above phenomena can be attributed to a renal internal secretion: They represent merely the effects of extracts of adrenal rests contained in renal tissue. Evidence to this effect is submitted in the section on the organotherapy of kidney substance on page 703 of the present volume. The existence of adrenal rests is the recognized source of hypernephromata (see page 129); indeed, Lewandowsky found that the effects obtained from renal venous blood differed in no way from corresponding quantities of venous blood obtained elsewhere in the body. As to the rise of temperature, the elevated blood-pressure, and the dyspnea, they are all typical effects of adrenal extracts. Fuchs and Roth[74] found that adrenalin increased markedly the intake of oxygen and the output of carbon dioxide, while Reichert, Lépine, and Morel noted that adrenal extracts increased the temperature along with the blood-pressure. Oliver and Schäfer not only demonstrated the latter phenomenon, but also the fact that adrenal extracts produced dyspnea and could even arrest respiration. This observation, which was recently confirmed by Langlois and Garrelon, is obviously due to toxic spasm of the respiratory muscles, the precursor of the convulsions witnessed. As to the benefit obtained with renal extracts, they were simply due to the detoxicatory action of the adrenal principle first pointed out by Langlois and now generally recognized. On the whole, the following conclusion seems to me warranted.

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[72] Bingel and Strauss: Deut. Archiv für klin. Med., B. xcvi, S. 476, 1909.

[73] Pearce: Archives of Intern. Med., March, 1912.

[74] Fuchs and Roth: Zeitsch. f. Pathol. u. Ther., B. x, p. 187, 1912.

No internal secretion of the kidneys exists; all effects of renal extracts witnessed are due to the adrenal principle the kidney normally contains.

What evidence is available tends to show that the kidneys are closely related functionally with the ductless glands and with the adrenals in particular.

As stated by Howell,[75] "the kidneys receive a rich supply of nerve-fibers," although "most histologists have been unable to trace any connection between these fibers and the epithelial cells of the kidney tubules." Interpreted from my viewpoint such a connection is not in the least necessary, since, as shown by Claude Bernard, the function of an organ is dependent upon the volume of arterial blood circulating through it. My view is fully sustained by the prevailing doctrine, since, as Howell says, the marked effects obtained during purely physiological experiments are "all explicable by the changes produced in the blood-flow through the organ." It becomes a question, therefore, as to how and by what nerves this blood-flow is regulated, for, as stated by Stewart,[76] "increased blood-flow entails increased secretion."

That the vasodilation necessary to the inception of an exacerbation of function—as it is in the submaxillary gland—occurs in the kidney as well as in the organs previously reviewed, is shown by the experiments of Bradford,[77] who found that vasodilator nerves entered the kidney with the vasoconstrictor fibers, and that when the anterior roots of the eleventh, twelfth, and thirteenth dorsal nerve roots were stimulated with induction shocks one second apart, the organ swelled though no sufficiently marked rise of blood-pressure occurred to account for it.

Stewart[78] also states that the presence of dilator fibers for the kidney has been "demonstrated in the splanchnic nerves." That it is these vasodilators which enhance the flow of urine is sustained by the prevailing opinion that true secretory nerves,

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[75] Howell: T. B. of Physiol., second edition, p. 763, 1907.

[76] Stewart: *Loc. cit.*, p. 419.

[77] Bradford: Jour. of Physiol., vol. x, p. 358, 1889.

[78] Stewart: *Loc. cit.*, p. 152.

i.e., nerves influencing directly the epithelial elements, are not present in the kidney.

The source of these renal vasodilator nerves is disclosed by the fact that it is only by stimulating the splanchnic that the caliber of the renal arteries is increased. Indeed, Eckhard[79] found that stimulation of the vagi below the diaphragm does not influence the flow of urine. This imposed the conclusion that even the vasodilators of the kidney belong to the sympathetic system. This is confirmed by the researches of Berkley[80] which showed that "the innervation of the kidney is dependent directly upon the great sympathetic; and histologically speaking, it is found that all the nerves of the glands belong to the non-medullated type." Briefly, the vasodilator nerves of the kidney which promote the flow of urine belong to the sympathetic system.

How are the arteries restored to their normal caliber—that compatible with the normal excretion of urine?

In the light of the conclusions submitted in the foregoing pages the kidneys should receive filaments capable of causing constriction of the renal arteries when the excretory activity of the organs is to be decreased. That such is the case has been shown experimentally by many observers. In the dog, the vasoconstrictor nerves leave the cord, according to Stewart, "by the anterior roots of the sixth thoracic to the second lumbar nerves and especially the last three thoracic." Langley[81] observed prompt and great pallor of the kidney and upper part of the ureter on stimulating the first lumbar nerve, and slower, though still great, pallor on stimulating the second lumbar in the cat. As stated by Starling[82] a rise of the general blood-pressure coincides with marked shrinkage of the kidney, so that the effects observed by Langley must be of vasomotor origin. Moreover various toxics known to raise the vascular pressure produce effects similar to stimulation of the renal vasomotor nerves. Thus Sakussow[83] recently found that digitalin in 1 to 1,000,000 solution caused contraction of the renal vessels.

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[79] **Eckhard:** Cited by Starling, Schäfer's "T. B. of Physiol.," vol. i, p. 645.
[80] **Berkley:** Jour. of Path. and Bact., vol. i, p. 406, 1893.
[81] **Langley:** Schäfer's "T. B. of Physiol.," vol. ii, p. 643.
[82] **Starling:** *Ibid.*, vol. i, p. 645.
[83] **Sakussow:** Vratch, April 10, 1904.

The same effect was obtained from a 1 to 1,000,000 solution of adrenalin. The latter result accounts for the fact that Bradford[84] obtained renal vasoconstriction by stimulating, besides the nerves included within the above limits, the fourth and fifth thoracic, thus including among those stimulated the fibers which pass to the splanchnic and thence to the kidneys. He found, however, that the most active vasomotor nerves were those of eleventh, twelfth, and thirteenth thoracic. That all these filaments are distributed to the arterioles in the organs has not only been established histologically, but, as stated by Böhm, Davidoff, and Huber,[85] "from the plexuses surrounding the vessels small branches are given off which end on the muscle-cells of the media.

As to the source of the vasoconstrictor fibers, it corresponds with that of the vasoconstrictors supplied to other abdominal organs, the splanchnic. Thus Nollner[86] and others have traced these nerves from the sympathetic chain through the great and small splanchnics to the solar plexus, and thence to a network of fibers lying in the fat between the adrenal and the kidney. Several of the filaments were found by Nollner to enter the latter with the renal artery.

We thus find ourselves in the presence of the surprising fact that both the vasodilator and vasoconstrictor nerves of the kidneys, those which preside over the functions of these organs, are of sympathetic origin. Indeed, as will be shown later, this is a characteristic of the adrenals, these organs and the kidneys working in harmony: the adrenals by supplying, as we have seen, the oxidizing substance of the blood, which takes part, among other functions, in the disintegration or proteolysis of waste-products in order to convert them into eliminable end-products; the kidneys, by insuring the excretion of these end-products from the system.

This accounts for various observations that present knowledge fails to explain. Thus Aubertin and Ambert[87] found concomitant lesions, both on naked eye and microscopical examination, in the adrenals and kidneys in all cases of nephritis studied by them characterized by high-pulse tension. The latter phenomenon suggests that while an excess of adrenal secretion was being produced—this product and adrenalin causing, as is well known, a marked rise of the vascular tension—the kidneys had also been overworked in these cases, *i.e.*, excessive excretory activity had brought on the nephritis. In other words, marked increased functional activity of the kidneys, as represented by renal vasodilation, should coincide—since the adrenals are simultaneously stimulated—with increased vascular tension. This has been actually observed experimentally by Cavazzani,[88] though unexplained by him. He found that urea caused simultaneously expansion of the kidney—and therefore an increased production of urine—and general vasoconstriction. Puncture of the floor of the fourth ventricle (Bernard's *piqûre*) produces glycosuria through the intermediary of the adrenals, as will be shown elsewhere; a similar puncture also produces, as stated by Stewart, "a copious flow of urine." We need not go beyond common experience to find ample proof of the fact that polyuria is a prominent symptom of diabetes, *i.e.*, that the adrenals and the kidneys work in harmony. The importance of this relationship asserts itself when the obscurity surrounding the question is recalled. Thus referring to polyuria, Hensell, Well, and Jelliffe[89] mention their observation that "it is common to two diseases—diabetes mellitus and chronic interstitial nephritis—but in either case a clear explanation of this symptom does not exist."

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[84] Bradford: Jour. of Physiol., vol. x, p. 358, 1896.

[85] Böhm, Davidoff, and Huber: *Loc. cit.*, p. 335, 1905.

[86] Nollner: Beiträge z. Anat. u. Physiol. v. Eckhard, B. iv, S. 139, 1869.

[87] Aubertin and Ambert: Tribune médicale, p. 119, 1904.

Pending additional evidence to this effect the following conclusions as to the functions of the kidney appear to us warranted:—

1. When the flow of urine is to be increased, the renal arterioles are dilated by vasodilator terminals of the sympathetic which reach the organ by way of the splanchnic nerves and the semilunar ganglia. The glomerular tufts being thus traversed by a greater volume of blood the components of urine are thus filtered out into Bowman's capsule.

2. When the flow of urine is to be decreased the same arterioles are reduced to their normal caliber by the vasoconstrictor

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[88] Cavazzani: Arch. ital. de biol., vol. xviii, p. 158.

[89] Hensel, Well, and Jelliffe: "The Urine and Fæces," 1905.

filaments of the sympathetic which reach the kidneys also by way of the splanchnic nerves.

3. The adrenals and the kidneys are functionally united, the adrenals contributing by their secretion to the conversion of waste-products into end-products which the kidneys excrete with the urine.

With the functions of the kidneys as complemental to those of the adrenals, what we have termed the "adrenal system" acquires greater importance in the vital functions of the organism as a whole: it supplies the body the substances which sustain oxygenation and metabolism, but provides also for the elimination of end-products of catabolism and other wastes. By "substances" here are meant both the adrenal and thyroid secretions. The former of these, by becoming oxygenized in the lungs, constitutes the oxidizing substance of the blood, *i.e.*, the albuminous portion of its hæmoglobin; the thyroid secretion as previously stated, and as will be shown, enhances the vulnerability of all tissues to oxidation, including the adrenal center in the pituitary body.

As to the functional relationship between all these organs, they may be briefly summarized as follows, pending additional evidence:—

The pituitary body contains a center which governs the functional activity of the adrenal system and of the kidneys. Any excitation of this center by certain toxics that may occur in the blood increases the functional activity of the organs of this system; the adrenals and thyroid apparatus, and also the kidneys, and, therefore, general metabolism and renal excretion.

The importance of this functional combination is self-evident. *While the adrenal system sustains metabolism, the kidneys, governed by the same center, can eliminate the waste products formed in the course of this process uninterruptedly as they appear in the blood.*

THE ADRENAL SYSTEM AND THE GENERATIVE GLANDS.

Testicles.—Leydig showed in 1850 that the interlobular connective tissue of the testicle contained epithelial cells. All evidence available tends to show that, in accord with the conclusions of Regaud and Policard,[90] confirmed repeatedly by other observers, these cells, which are situated between the seminiferous tubules, are the source of the internal secretion which endows the body with the male characteristics. The Leydig cells are functionally united with the sperm-cells, and, as shown by Regaud and others, undergo considerable development prior to spermatogenesis. Besides this functional connection with the latter process, their secretion is supplied to the organism at large, through the intermediary of the lymph- or blood- vessels.

The influence of the internal secretion of the cells of Leydig on the body at large is well shown by the influence of early removal of the testes, *i.e.*, castration. A tendency to obesity of a feminine type, due to slowed catabolism of fats, scantiness of hair, deficient development of the thorax, pelvis, and larynx, the voice remaining high pitched as in the child. The muscles lose their tone and the prostate and vesiculæ seminales fail to develop, the bones of the extremities, however, growing abnormally long. The mental attributes of the male sex are also lacking; while the intelligence may be normal, there is absence of aggressiveness and initiative and intellection is slow. As stated by Schaefer,[91] "the effects are mainly upon metabolism, although the limit of assimilation of carbohydrates is lowered."

While the effects of castration on man and the lower animals are well known, the manner in which they are produced has remained obscure. Analysis of the question has led me[92] to suggest that the testicles did not produce a true internal secretion, but that the adrenal rests (interrenal tissue) which they contain contribute to the elaboration of the sperm; and, moreover, that when *through sexual abstention the secretion is unused, it is taken up by the circulation and distributed throughout the body, producing the effects of the adrenal secretion* (*in organic combination*) *upon the tissues at large.*

The presence of interrenal tissue or adrenal rests in the testicle is well known. Wiesel[93] found it imbedded in both the testicular tissue and in the paradidymis. These correspond with the cortical portion of the adrenals, the cytoplasm of the interstitial cells containing also the lipoid granules, blackened by osmic acid (Schaefer[94]), and also, according to Reinke,[95] crystals the nature of which is unknown. The medullary portion of the adrenals is also represented as a constituent evidently of the seminiferous tubules or sperm-cells, since spermin (isolated by Poehl) gives the reaction, chemical and physiological, of adrenalin. Thus spermin was identified by Poehl as an oxidizing body, acting catalytically, a property I had attributed to the adrenal principle. As is the case with the latter also, spermin resists heat up to, and even, boiling; it is insoluble in ether and practically insoluble in absolute alcohol, and gives the guaiac, Florence, and other hæmin tests. It likewise raises the blood-pressure, slows the heart, and produces all other physiological effects peculiar to the adrenal principle. Moreover, it is regarded in Europe as a powerful "oxidizing tonic" and has been found equally useful in disorders in which adrenal preparations had given good results. As does adrenalin, it produces quickening of the respiration, while large quantities inhibit it, as shown by Dixon, Langlois, and others.

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[90] **Regaud and Policard: C.-r. de la Soc. de Biologie, April, 1901.**
[91] **Schaefer: "Lane Medical Lectures," p. 988, 1913.**
[92] **Sajous: New York Med. Jour., Sept. 4, 1909.**
[93] **Wiesel: Sitzamgsberichte d. k. Akad. z. Wien, S. 108, 1899.**

Its independence of any connection with sex characteristics is shown by the fact that it has been found in the blood of females as well as in that of males.

Additional testimony is afforded by the fact that while, as stated by Hansemann,[96] "the cells of Leydig are concerned in the production of testicular tumor," the characteristic effects of such tumors on the organism at large are precisely those produced by a tumor of the adrenal cortex, or of adrenal rests in the kidney, which represent 17 per cent. of the tumors of this organ. These tumors, as we have seen under a previous heading, cause in children abnormal sexual and physical development, with marked increase of strength, abnormal growth of hair over the pubis, axillæ, legs, and trunk, lowering of the voice,—an aggregate of anomalies which cause a child of 5 years, for instance, to be transformed into a young adult in weight, strength, sexual development, etc. (See the illustration on next page.) Now, as to the testicular growths Schaefer[97] writes: "Remarkable cases have been described in both male and female sex in which tumors of the testicle and ovary, apparently malignant in character [see page 131 of this volume for corresponding symptoms in malignant hypernephroma], occurring in children, have been accompanied by a general growth of stature and by premature appearance of secondary sexual characters such as growth of hair on the face in the male and in the armpits, and on the pubes in both sexes, development of breasts and generative organs: in short, all the signs of puberty, which, on removal of the tumor, have been found to disappear."

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[94] Schaefer: *Loc. cit.*, p. 88.

[95] Reinke: Archiv f. mik. Anat., B. 42, 1896.

[96] Hansemann: Cited by Biedl, "Internal Secretory Organs," p. 396, 1913.

[97] Schaefer: *Loc. cit.*, p. 90.

PENILE TRANSFORMATION OF CLITORIS AND ADULT HIRSUTIES DUE TO HYPERNEPHROMA IN GIRL OF SEVEN YEARS. (*Jump, Beates, and Babcock.*)

The presence of spermin in the blood of females referred to above is an important feature of the problem as a whole, for it shows that its chemical homologue, the adrenal product, is the determining factor of sex production. Thus we have seen (page 302) that tumors of the adrenal cortex caused females to undergo changes toward male characteristics, male organs having become sufficiently developed in 10 of the women referred to by Apert as to cause them to live as men. This transformation is well shown in the above cut, illustrating the case described on page 301, reported by Jump, Beates, and Wayne Babcock. Suggestive also in this connection are the experiments of Allen J. Smith and W. J. Crocker,[98] who found that by injecting a salt-solution extract of a cock's testis into hens these animals showed many indications of assuming male characteristics. The comb in most cases increased in size and brightened, the wattles likewise. In some of the hens the neck feathers became somewhat more brilliant, the same peculiarity applying to the small feathers at the base of the tail. In one hen a slight but distinct growth of spurs was recognized. Some of the hens became combative, and several times they attempted to cover other hens after the manner of the cock.

On the whole it seems clear that *it is to the secretion of adrenal tissues, wherever situated, that the male characteristics are due.* This phenomenon finds a ready explanation in my view that the adrenal secretion supplies the blood the oxidizing ferment which as a catalyzer endows living tissues with their vital dynamism.

Dixon,[99] after using orchitic injections, concludes that the effects observed were due to its nucleo-albumin. Orchitic extracts are known to contain nuclein, a ferrinuclein according to Cavazzani,[100] in the proportion of about 2.4 per cent. But this applies to semen, in which spermatozoa and other substances containing nuclein are present. Still, absence of functional testes being known to produce abnormalities of the bones, it is probable that the thymus is involved in the process. This is further suggested by the fact that Hatai[101] found that in white rats removal of the sex glands caused the thymus to increase to almost twice its size. This feature of the process belongs to the generative sperm-cells, and not to the interstitial cells of Leydig.

With the so-called internal secretion of the testicle identified as a product of adrenal rests in this organ, and recalling the action of the adrenal product upon oxidation, metabolism, the vascular tension, etc., we can understand the morbid effects of masturbation and excessive venery—particularly the debility, languor, mental torpor, and deficient growth in boys addicted to these habits. These symptoms coincide with those which, we have seen, follow castration. Bouin and Ansel[102] have shown, moreover, that extracts of interstitial tissue counteracted the effects of the latter operation and tended to promote growth.

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[98] Smith and Crocker: New York Med. Jour., July 5, 1913.

[99] Dixon: British Med. Jour., Sept. 21, 1907.

[100] Cavazzani: Gazzetta d. Osp. e d. Cliniche, June 28, 1903.

[101] Hatai: Jour. of Exper. Zoölogy, Jan., 1915.

On the whole the above data seem to warrant the following conclusions:—

1. *There is no true internal secretion of the testes, the products of the epithelial (Leydig's) and seminal cells which unitedly take part in the formation of the seminal fluid, being derived mainly from adrenal rests in those cells.*

2. *When seminal fluid is not secreted during coitus, masturbation, etc., that part of it contributed by the epithelial and seminal cells is added to the asset of adrenal products in the body at large.*

OVARIES.—There is considerable analogy between the characteristic effects of castration in the male and those following removal of the ovaries in the young. What remains of the genital organs, the uterus, vagina, and vulva, and also the breasts, retain their infantile type. In developed females this operation tends to produce atrophy of the same structures and obesity (also observed in men after castration), menstruation meanwhile ceasing. The influence of the ovaries on metabolism also corresponds with that of the testicles. The dictum of Brown-Séquard,—to whose remarkable physical improvement under the influence of testicular extract I can bear witness,—that this agent is more efficient than ovarian extract in the treatment of women, suggests a kinship between these two organic substances. This is emphasized when the pharmacological action of ovarian extract is considered. It raises the blood-pressure and slows the heart, as shown by Fedoroff,[103] Jacobs,[104] and others. Removal of the ovaries, moreover, reduces the oxygen intake 10 per cent., as shown by Loewy and Richter,[105] while ovarian extract restores it; it has been, therefore, regarded as an oxidizing ferment. Neumann and Vas[106] noted that ovarian extract enhanced metabolism; Senator observed that ovarian preparations increased diuresis and the excretion of urea and phosphoric acid. Its physiological effects are those of adrenal preparations, therefore, in every respect.

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[102] Bouin and Ansel: C.-r. de l'Académie des Sciences, Jan., 1904.

[103] Fedoroff: La Gynécologie, Oct. 15, 1891.

[104] Jacobs: Dublin Jour. of the Med. Sci., Sept. 1, 1897.

[105] Loewy and Richter: Berlin. klin. Woch., Bd. xxxvi, S. 1095, 1899.

[106] Neumann and Vas: Monats. f. Geburtsh. u. Gyn., Bd. xv, S. 433, 1902.

Its effects on oxidation are so striking, in fact, that they have been clearly recognized by many clinicians. "We are authorized to classify ovarian organotherapy among the oxidizing agents," write Dalché and Lépinois.[107] "This conclusion, it must be admitted, is that reached by several authors. Curatello and Tarulli believe that the internal secretion of the ovaries favors the oxidation of phosphorized organic substances, hydrocarbons, and fats. According to Gomes, it enhances oxidation and hydrolysis and favors the elimination of phosphates. . . . Albert Robin and Maurice Binet have shown that there is during menstruation an increase of the respiratory exchange. Keller, studying the general exchanges, found that there was increased nitrogen oxidation. We have ourselves found that menstruation, in itself, enhances vital functions and particularly the great function of general oxidation." Sauvé[108] states that ovarian extract increases the hæmoglobin content of the blood.

To which of the ovarian tissues, the Graafian follicles, the corpora lutea, or the interstitial cells, must this pharmacological action be attributed?

According to Mulon[109] (1904), the *corpus luteum* presents all the morphological characteristics of an aggregate of chromaffin cells, to which class the cells of the adrenal medulla also belong. Indeed, Prenant[110] found that, both in origin and histological structure, the corpus luteum, which remains after elimination of the ovum, shows all the characteristics of an internal secretion gland. Schaefer states that its extreme vascularity suggests that its product passes into the blood. This would explain its influence upon distant organs such as the mammary glands; Ancel and Bouin[111] having shown that the development of the latter coincided with that of the corpora lutea, and that destruction of these bodies arrested the development of the mammary gland. The corpora lutea are endowed, however, with other important functions. According to Bandler, it assists not only in the preparation of the uterine mucosa for the formation of the uterine deciduum and in the reception and fixation of the ovum, but also, as first shown by Prenant,[112] and in common with the ovary proper, it serves to protect the maternal organism against the destructive local activities of the parasitic ovum and its placental secretion. When impregnation does not take place, the proliferation of the lutein cells occurs only during the few days which the menstrual cycle lasts.

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[107] Dalché and Lépinois: Bull. Génér. de Thérap., Jan. 8, 1902.

[108] Sauvé: Paris Médical, April 1, 1911.

[109] Mulon: C.-r. de la Soc. de Biol., vol. lvi, p. 113, 1904.

[110] Prenant: Revue Générale des Sciences, 1898.

[111] Ancel and Bouin: C.-r. de la Soc. de Biol., vol. lxvii, p. 466, 1909.

The corpora lutea are formed, as is well known, after the discharge of the ovum, in the *Graafian follicles,* the lining of which forms folds and becomes permeated with blood-channels. When pregnancy occurs, the epithelium of the Graafian follicles proliferates, its cells increase in size and become filled with yellowish granules: the corpora lutea. The follicles have been credited with the power to promote the nutrition of the uterine mucosa and to initiate the premenstrual congestion of the latter. From my viewpoint all these functions are to be attributed to the corpora lutea of the Graafian follicles; though by "function" here I mean only the part the former play as chromaffin cells (of which, we have seen, they possess all the morphological characteristics) in reactions with other agencies. What is the nature of these bodies?

A suggestive fact is that the structure described by Bouin[113] as the *interstitial gland* is known to fulfill various functions attributed also to the corpora lutea. It becomes enlarged during menstruation as well as during pregnancy, thus sustaining sexual life up to the menopause. It attains its highest development during the pregnant state, beginning with the nidation of the fertilized ovum in the uterus. Located in the ovarian stroma, interstitial cells have been found to maintain the nutrition and integrity of the uterus, through some process as yet undetermined.

From my viewpoint, this process is explained through various facts brought out in the course of our analysis of testicular internal secretions, and the conclusion submitted that adrenal rests, medullary and cortical, constitute the so-called internal secretions of these organs. Thus, Limon,[114] quoted by Biedl,[115] found that "the interstitial tissue of the ovary is composed of epithelial cells, the protoplasm of which is filled with granules resembling fat which stain black with osmium. These cells are differently placed in different animals; they are sometimes arranged in compact masses and cords." Now, this description applies precisely to the cortical portion of the adrenals. Indeed, this similarity had been noted by others than myself in respect to the ovaries. "That the interstitial stroma cells possess a secretory function is suggested," also writes Biedl, "by the presence of fat granules and other secretory enclosures, as well as by certain resemblance, commented upon by many (Mulon, Wallart), to the cells of the suprarenal cortex."

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[112] Prenant: *Loc. cit.*

[113] Bouin: Revue médicale de l'Est., vol. of 1902.

Although Bouin gave the ovarian cells of this type the name of "interstitial," they do not correspond with the interstitial or Leydig cells of the testicle, which, as Schaefer states, "show, when present, many analogies with the cells of the corpora lutea." This physiologist also expresses the opinion that the corpora lutea appear not to be concerned with the secondary sex phenomena. Interesting in this connection is what has been termed, "a remarkable instance of the correlation of the corpus luteum with the secondary sex characters" described by Pearl and Surface,[116] of the Maine Agricultural Experiment Station. A cow which had produced three calves and given an abundant flow of milk suddenly ceased to produce the secretion from the mammary gland. The udder rapidly shrank to a small size and the animal began to show the external characteristics of a bull. After a lapse of eight months the assumption of the male characters in various regions of the body was complete and perfect. A necropsy showed, as the only gross abnormality, a simple cystic condition of the ovaries. Histologically and cytologically these organs differed from the normal cow's ovary in only one essential respect, namely, that they had no corpora lutea, thus leaving the interstitial cells intact. If *absence* of corpora lutea played any rôle in the process it could only be a passive one which endowed the "interstitial organ" of the ovary with *active* rôle. Such being the case, and the interstitial gland corresponding, as observed by Mulon, Wallach, and myself, with the adrenal cortex, we are brought to realize that *the secondary sex characteristics are attributable, in the female, to the ovarian interstitial cells, which correspond morphologically and chemically with those of the adrenal cortex.*

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[114] Limon: Archives d'anat. microscop., vol. v, fasc. II, Sept., 1902.

[115] Biedl: "Internal Secretory Glands," p. 399, 1913.

[116] Pearl and Surface: Science, xli, p. 615, 1915; Jour. Am. Med. Assoc., July 14, 1915.

On the other hand, the foregoing analysis tends to show that *the interstitial cells of the female are not the same structures as the interstitial (Leydig) cells in the male; the Leydig cells, connected functionally as they are with the sperm-cells, correspond with the Graafian follicles and their corpora lutea, as secreting structures.*

On the whole, however, and in keeping with conclusion 1 submitted in respect to the testicles: *There is no true internal secretion of the ovaries, the products of the Graafian follicles and their corpora lutea and of the interstitial stroma-cells being derived mainly from adrenal rests in those cells.*

Here, however, the physiological rôle of the testicular products cannot be reproduced, for if, as in the male, the products of the adrenal rests were absorbed when not secreted through sexual congress, masturbation, etc., the male characteristics would assert themselves in the female through the accumulation of the secretion of her interstitial cells. Hence, *to provide against the loss of female characteristics through accumulation of the secretion of the inerstitial glands in the body at large, the products of the ovarian adrenal rests are eliminated periodically,* i.e., *during the menstrual cycle.*

It is because of this fact, as we have seen, that the loss of the testicular glands causes in the male the appearance of female characteristics, while in the female the accumulation through tumors, etc., of adrenal cells, causes the development of male characteristics.

Finally, when pregnancy occurs, all the dynamism which the adrenal rests provide through the influence of their secretion, acting mainly as catalyzer, on oxidation, become necessary for the development of the new being, lactation, etc., and the menstrual cycle ceases.

CHAPTER X.

THE POSTERIOR PITUITARY AS A GENERAL NERVE-CENTER AND AS CO-CENTER OF THE ANTERIOR PITUITARY IN SUSTAINING LIFE.

THE IDENTITY OF THE LOWER BRAIN.

In the earlier editions of this work I urged that certain centers in the medulla oblongata were probably but subsidiary centers which received nervous impulses from the pituitary body by way of the tuber cinereum and other basal structures. I held, moreover, that "inhibition" as obtained by physiologists represented a pathological phenomenon in that it was caused by excessive constriction of the cardiac arterioles provoked by vasoconstrictors contained in the nerve stimulated, the vagus.

As is well known, it was the work of the brothers Weber (1845) which first suggested that the heart could be "inhibited" by stimulation of a definite region in the medulla. Their experiments differed from those we have reviewed in that the tissues of the base of the brain were traversed by the current, thus exciting structures in which we have seen sympathetic and other nerves pass from the pituitary to the bulb. One pole having been placed in the nasal cavity of a frog and the other on the spinal cord over the fourth or fifth vertebra, the heart's action momentarily ceased, then gradually resumed its normal activity. Approximation of the poles upon the cerebral hemispheres and stimulation of the cord produced no effect upon the heart. "Not until the medulla oblongata between the corpora quadrigemina and the lower end of the calamus scriptorius was stimulated," says William T. Porter, "did the arrest take place. Cutting away the spinal cord and the remainder of the brain did not alter the result." The level of fibers from structures below the brain is also suggested by the effects of experimental injury of the bulbar area which Flourens termed *le nœud vital*.

Galen had already noticed that death ensued when a certain spot in the floor of the fourth ventricle close to that which is now known as the center of the vagus was injured. But Legallois and Flourens have added much to our knowledge of its physiological relations, and the spot in question, as we have seen, is still considered as the respiratory center. "The results of various investigations show, however," says Reichert,[1] "that Flourens's area, as well as certain other parts of the medulla oblongata that have been looked upon by others as being respiratory centers, are not such, but are largely or wholly collections of nerve-fibers which arise chiefly in the roots of the vagal, spinal accessory, glosso-pharyngeal, and trigeminal nerves, and which, therefore, are probably nerve-paths to and from the respiratory center. Moreover, excitation of the '*nœud vital' does not excite respiratory movements*, but simply increases the tonicity of the diaphragm; nor is the destruction of the area always followed by a cessation of respiration. While the precise location of the center is still in doubt, there is abundant evidence to justify the belief in its existence in the lower portion of the spinal bulb." That we are again dealing with the aggregate of centers to which the pituitary body projects its fibers suggests itself. Flourens located his "vital knot" in an area five millimeters wide *between* the nuclei of the vagus and spinal accessory nerves—again in the *lower end of the calamus scriptorius: i.e.*, a region comprised in the area to which the Weber brothers applied one electrode, the other being in the nose, when cardiac arrest or inhibition was first observed by them.

An interesting relationship seems to me to exist between these two sets of experimental results. Indeed, the area to which the pituitary body sends its fibers thus becomes the source of antagonistic effects involving the same structures: *i.e.*, the Weber brothers caused arrest of the heart by causing undue constriction of its coronaries and ischæmia of the myocardium, in the manner previously described, while the lesion produced by Flourens in the same area, when sufficiently severe, blocked the flow of impulses to and from the heart. Flourens's *nœud*

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[1] Reichert: *Loc. cit.*

vital, therefore, is no more the respiratory center than the area traversed by the current can be called an "inhibitory" area. We are simply dealing with the results of two morbid factors: overstimulation (Weber) and interruption (Flourens) of physiological—and therefore functional—impulses transmitted *through* the medulla and the cord.

In the fifth chapter reference was made to the fact that the posterior pituitary lobe alone, as shown by Howell, contained an active principle. This lobe, the "infundibular," has long been termed the "neural" portion of the whole organ, and appears to me to present anatomical features that further suggest a direct connection between it and the cerebro-spinal centers. Hence the use of the words "physiological impulses transmitted *through* the medulla and the cord." The question becomes all the more worthy of a searching inquiry, inasmuch as a casual examination of the mutual relations, anatomical and physiological, of the cerebral structures traversed by the current in the experiment of the Weber brothers suffices to show that the elements thus submitted to excessive stimulation coincide with those which would normally fall under the influence of the posterior pituitary body.

The physiological characteristics of the parts influenced by the current must first be ascertained. In the frog, the distance between the nose and the medulla being very short, a current would implicate all elements in its direct path, considering the character of the structures traversed. In this animal, the lizard, etc., the nasal nervous terminals, the tissues about the floor of the median ventricle and the habenula, appear to me as the paths that would be involved. In man the distance between the olfactory area or the nasal subdivisions of the fifth pair and the medulla is also relatively limited, and the intervening structures are of such a nature as to also allow the current to pass uninterruptedly in a straight path. But the floor of the median or third ventricle, which in its anterior portion overlies the base of the skull and is very thin, becomes what appears to be the inevitable path of free conduction, owing to this proximity of the olfactory bulb and the trigeminal nasal terminals to the medullary centers. Of special interest here, however, is the fact that in man (and to a great extent in the frog) the first structure reached by the current after the nasal structures would be the infundibular portion of the third ventricle: *i.e.*, that connected with the posterior pituitary lobe. Again, and very suggestive, is the fact that these structures and all those falling in the line of the current form part of what Professor Foster terms "in point of origin the oldest part of the brain" and "the central gray matter" which "seems to serve chiefly as a bed for the development of the nuclei of the cranial nerves." Indeed, we might repeat that, as stated by Reichert,[2] "one center has been located in the rabbit in the *tuber cinereum,* which has been named a polypnœic center because, when excited, the respirations are rendered extremely frequent." . . . "Another area has been located in the optic thalamus, in the floor of the third ventricle; this center," says the author, "is believed to be excited by impulses carried by the nerves of sight and hearing, and when irritated causes an acceleration of the respiratory rate."

The more dorsal portion of the current would strike a no less important physiological region. "Next to the central gray matter," says Professor Foster, "and more or less associated with it, comes what is called the tegmental region, of which the reticular formation coming into prominence in the bulb and continued on to the subthalamic region forms, as it were, the core. Belonging to the tegmental system are numerous masses of gray matter from the conspicuous optic thalamus and the red nucleus in front to the several nuclei of the bulb behind. This complex tegmental system, which may, perhaps, be regarded as a more or less continuous column of gray matter, comparable to the gray matter of the spinal cord, serves as a sort of *backbone to the rest of the central nervous system.*"

The morbid effects of the current become normal consequences when we consider that the structures traversed by it include those that even emotions will disturb. Referring to the posterior portion of the pons, that adjoining the tissues that form the fourth ventricle and which represents the downward continuation of the tegmentum, Professor Duval says: "It is, indeed, to the pons that we seem to be authorized to attribute the most important rôle in the greater emotional expressions, laughing and weeping, cries of pain: in a word, involuntary manifestations." That the structures such as those penetrated by the current should be suddenly jarred and forcibly thrown into vibratory conditions entirely foreign to their normal vibratory rhythm is manifest. That such jarring, especially when the current follows axially a direction opposite to that of a physiological stream of impulses, should so pervert its normal influence upon the organs to which these impulses are normally distributed—heart, lungs, stomach, etc.—as to temporarily or permanently arrest their functions is not only logical, but in accord with the known effects of electricity upon the more highly developed structures.

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[2] Reichert: *Loc. cit.*

And we can also doubtless better understand why respiration still continues very much as usual after removal of the brain above the medulla, and why, indeed, all nervous manifestations other than ideation can persist after such mutilation. While there is no *"nœud vital,"* or ganglion of life, in the sense given these words by Flourens,—*i.e.*, in the spot of the medulla where injury arrests respiration,—and the area so injured is not "the mysterious seat of the unknown principle of life," there is, nevertheless, in this location, not a *locus minus resistentiæ,* but an aggregation of nervous paths from all directions, which an injury can functionally impair or destroy, according to the quantity of tissue involved and the kind of lesion produced. Flourens doubtless caused death; but in looking for death in his experimental animals he doubtless did not treat the *"nœud vital"* with the gentleness of a dove. Death ensued—the result of conditions similar to those produced by the Weber brothers with electricity in the sense that molecular disturbance was produced. Yet the Weber brothers only jarred the naso-bulbar structures, and produced temporary inhibition of cardiac action; being more diffuse, the current spread over greater bulbar surface and did less injury. Flourens's puncture, on the contrary, produced an organic lesion, capable not only of destroying the tissues involved, but also of annulling, by the circumferential compression of the neighboring elements caused, the functions over which the latter preside. Even the process of repair, which at once begins under such conditions, may lead to a fatal issue, the infiltration throttling, as it were, the paths *to* and *from* organs through which life is sustained. When we consider the small relative size of the fourth ventricle, and the fact that the so-called "vital knot" is located in an area which may be computed only by a few millimeters; when we furthermore recognize that such an injury would thus include the vagal, spinal accessory, glosso-pharyngeal, and hypoglossal within its radius of morbid influence, death as an injury to the spot becomes a normal consequence. The heart and the entire respiratory system—to refer only to those directly concerned with life's processes—are the mechanisms first functionally arrested.

And yet while obstruction of these few square millimeters of bulbar elements will rapidly destroy life, it is possible, says Professor Foster, in the case of some animals "to remove the cerebral hemispheres and to keep the animal not only alive, but *in good health* for a long time—days, weeks, or even months after the operation!"

There must prevail in this connection, however, another contradictory interpretation of experimental phenomena. Indeed, how can we reconcile the presence of motor *centers* in the cerebral cortex with the ability of an animal from which both hemispheres have been removed to execute the motions ascribed to these areas? That an animal deprived of its hemispheres will do this is graphically shown in the following lines of Professor Foster's: "We may, perhaps, broadly describe the behavior of a frog from which the cerebral hemispheres only have been removed by saying that such an animal, though exhibiting no spontaneous movements, can by the application of appropriate stimuli be induced to perform all, or nearly all, the movements which an entire frog is capable of executing. It can be made to swim, to leap, and to crawl. Left to itself, it assumes what may be called the natural posture of a frog, with the forelimbs erect, and the hindlimbs flexed, so that the line of the body makes an angle with the surface on which it is resting. When placed on its back, it immediately regains its natural posture. When placed on a board, it does not fall from the board when the latter is tilted up so as to displace the animal's center of gravity; it crawls up the board until it gains a new position in which its center of gravity is restored to its proper place. Its movements are exactly those of an entire frog except that they need an external stimulus to call them forth." It is quite clear that all motor phenomena are carried out, notwithstanding the absence of parts of the brain which have been undeniably shown by experiments in animals, pathological conditions of the human hemispheres, etc., capable of inciting them. The familiar convulsive movements in various parts of the body trunk, leg, arm, etc., when certain motor areas are stimulated would mean nothing to us if the use of electricity for this purpose were the basis of this doctrine, but *lesions* in these areas have unquestionably proven that they do preside over motor functions, not only in a general way, but in the sense implied by "cerebral localization." How account for the self-evident discrepancy which the entire absence of these structures indicates in present conceptions of the processes involved?

We are brought nearer to a solution when the removal of cerebral tissues—those to which I have referred as jarred by the electric current passed by the Weber brothers between the nose and the bulb—is continued downward until the cord only is left. "Very marked is the contrast," says Professor Foster, "between the behavior of such a frog which, though deprived of its cerebral hemispheres, still retains the other parts of the brain, and that of a frog which possesses a spinal cord only. The latter when placed on its back makes no attempt to regain its normal posture; in fact, it may be said to have completely lost its normal posture, for even when placed on its belly it does not stand with its forefeet erect, as does the other animal, but lies flat on the ground. When thrown into water, instead of swimming it sinks like a lump of lead. . . . When a board on which it is placed is inclined sufficiently to displace its center of gravity it makes no effort to regain its balance, but falls off the board like a lifeless mass." Such a frog moves its limbs irregularly, but one has but to witness such motions to at once conclude that they are aimless, mere random expressions of the inherent power to contract possessed by all muscular tissues, and which even persist some time after death, especially in the case of the heart-muscle. Very marked is the contrast, indeed, between this animal and one still endowed with the tissues of the base of the brain. "Pigeons, for instance, have been kept alive for five or six weeks," says the same author, "after complete removal of the cerebral hemisphere with the exception of portions of the crura and corpora striata immediately surrounding the optic thalami." . . . "In warm-blooded animals, as in the more lowly cold-blooded frog, the parts of the brain *below or behind* the cerebral hemispheres constitute a nervous machinery by which *all the bodily movements* are carried out."[3]

That this mechanism is located below the hemispheres in man has also been illustrated by many cases reported, among which may be cited the famous crow-bar case, in which, "by a premature explosion of gunpowder, an iron bar three and a half feet long, one and a quarter inches in diameter, and weighing thirteen and a quarter pounds, was shot completely through a man's head, and perforated his brain. This man walked up a flight of stairs after the accident, and gave his account of how it happened. Although his life was naturally despaired of for some time, he *developed no paralysis;* nor did marked impairment of his intellectual faculties follow convalescence. Eventually he recovered his health. Twelve years elapsed before his death, during which time he was a laborer on a farm."[4] This pointedly suggests that while the cerebral hemispheres from the lowly frog to the highest mammal can only awaken motion through volition, *i.e.*, voluntary movements, *the base of the brain—the pituitary body as we will see—can automatically govern motion through the intermediary of spinal gray matter.*

A remark which in this connection is of particular interest to us is that of Professor Duval, when, referring to the meaning of bulbar functions, according to modern conceptions, he says: "For the physiologist, the medulla extends above the limits of the vertebral column into the cranium and *about up to* the sella turcica. " *I* would say *into* the sella turcica, for it seems clear to me that *the posterior pituitary lobe presents*

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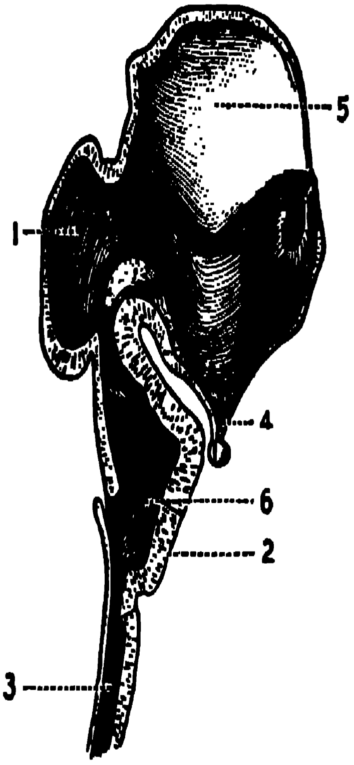
[3] The italics are my own.

[4] A. B. Ranney: "Lectures on Nervous Diseases."



MEDIAN AND VERTICAL SECTION OF A THREE MONTHS' EMBRYO. [Magnified.]

1, Aqueduct of Sylvius. 2, Medulla Oblongata. 3, Central Canal. 4, Infundibulum and Pituitary Bodies [the latter have been added to the original]. 5, Optic Thalamus. 6, Fourth Ventricle.

the functional characteristic that would fulfill the requirements of the complemental processes that the functions of the hemispheres demand.

The annexed colored plate, which represents a median and vertical section of the encephalon and bulb of a three months' embryo, distinctly indicates the direct continuation of the cord up to the posterior or infundibular pituitary lobe. The tract connected with the posterior pituitary is colored bluish gray. The pituitary has been added to the infundibular extremity of the original illustration. The relations of the structures which ultimately become the corpora quadrigemina by meeting the posterior part of the third ventricle are well shown.

That my views in this connection are based on a solid foundation is further sustained by the painstaking investigations of Andriezen,[5] who traced a direct connection between the pituitary and the medullary and other more anterior structures through the various phylogenetic stages of vertebrates. The following statements and the table appended are quoted from his paper: "A survey and investigation based on all classes of vertebrates show that the hypophysis occupies the position and relationship to the other structures which may be condensed in the following table:—

"RELATION OF PITUITARY TO OTHER NERVE-CENTERS AND HEAD-STRUCTURES IN ORDER FROM BEFORE BACK."

Nerve-center.	Olfactory center.	Posterior lobe of pituitary.	The bulbo-spinal centers.
Nerves.	Olfactory nerves.	Hypophyseal nerves.	Bulbo-spinal nerves.
Distribution.	Epithelium of nasal sac.	Pituitary duct gland (anterior lobe).	Buccal, etc., and general subcutaneous.
Body-region.	Pre-oral (prostomial).	Oral.	Post-oral (branchial, etc.) and general body."

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[5] Andriezen: British Medical Journal, Jan. 13, 1894.

Of course, this applies to both pituitary bodies, but I have shown that the anterior lobe could originate motor impulses in the partition separating it from the posterior lobe, and transmit them via the latter, the basal tissues, the bulb, the cord, the sympathetic chain and finally the splanchnic nerve to the adrenals. That the investigations of Andriezen, though sustained by the previously recorded results of removal of the pituitary by Vassale and Sacchi,[5a] should have borne but little fruit, so far, is probably accounted for by his statement that "variations in weight bring it under the Darwinian law of panmixia; if so, the indication being, what study of lower vertebrates shows, namely: that it has probably passed the acme of its activity and in man is functioning less vigorously."

I must express the belief, however, that, when man is in question, cessation of natural selection may not always mean that an organ has become useless, but instead that it has reached the acme of perfection. Loss of functional vigor may denote, in this connection, what it denotes in the human hand as compared to that of the gorilla: *i.e.*, gain in functional precision and delicacy.

In the embryo, the posterior pituitary body opens directly *into* the third ventricle through the infundibulum. If during uterine existence "the whole life-achievement of myriads of generations of living things" is represented, the phylogenetic history of this organ should show traces of its ultimate functions. Andriezen found that in the amphioxus its analogue is represented by "a subneural glandular organ, a duct lined by ciliated epithelium which affords a communication between the buccal and neural cavities, and a group of nerve-cells around and at the back of the upper opening where the duct widens into the ventricular cavity." We have here the main primitive structures of the pituitary in man.

Referring to Andriezen's investigations, Berkley[6] says: "He has farther shown that particles of carmine, suspended in the water surrounding the animals, will be taken up with the water *passing through the infundibular duct* and carried by ciliary action *into the ventricle,* and thence into the *central*

[5a] Vassale and Sacchi: Rev. Sper. di Fren., p. 83, 1894.
[6] Berkley: Brain, Winter, 1894.

canal of the cord; finally the particles of carmine may be traced right up to the free end of the canal, where the spinal cord opens into the exterior by the blastopore; therefore it is made manifest that the infundibular duct carries a stream of oxygen-bearing water for the nutrition of the tissues and the carrying off of their effete products." Alluding to personal studies to which I will presently refer, Berkley then adds: "It is quite curious to find essentially the same structures preserved in as high a vertebrate as the dog, and descending to so low a zoological order as amphioxus, though, as Müller remarks, the pituitary is practically the same *from myxine to man.*" Yet in man the infundibular orifice is *closed,* and the posterior pituitary, during its evolution, must, therefore, have assumed some function other than that possessed by the organ during the earlier phases of its career and of which the earlier forms should also show traces.

We have seen that oxygenation of the blood, the highest development of the function carried out by the water-vascular system in the amphioxus, belongs to the domain of the anterior pituitary. The remaining inference afforded by the phylogenetic history of the organ, therefore, is, in my opinion, that *the group of nerve cells* around and behind the upper opening *which in Amphioxus and Amocœtes forms the threshold of the oxygen-bearing water system is the prospective adrenal center in the human pituitary,* which center, we have seen, is also concerned with oxygenation.

I must state that I consider this perfect concordance between the functions of the anterior and posterior pituitaries as I have conceived them and those found throughout the entire evolutional scale of zoological forms as far back as the amphioxus by Andriezen as very strong evidence that my views are sound.

HISTOLOGY OF THE POSTERIOR PITUITARY BODY.

What is the physiological relationship between the two lobes? Déjerine[7] states that vertical and horizontal sections of both organs show that they are absolutely distinct and separated by a fibrous lamina; and, furthermore, that "the posterior lobe alone is connected with the infundibulum." . . . "It is developed from the brain" and "is a dependence of the middle ventricle." The anterior lobe is only connected with the cerebral structures through vessels which, according to Berkley,[8] "directly pass into it from the *substance* of the infundibulum." The blood-supply of the posterior lobe is also derived from the same source, but it is less rich, though sufficiently so to satisfy the needs of an active function. Indeed, the organs differ mainly in the character and wealth of their nerve-supply—much to the advantage of the posterior lobe, however. The development of the anterior lobe from the ectoderm of the primary oral cavity, instead of, as in the case of the posterior lobe, from the embryonic brain, accounts for what anatomical dissimilarities prevail.

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[7] Déjerine: "Anatomie des Centres Nerveux," vol. I, 1895.

The histological characteristics of the posterior lobe also suggest that it is the seat of some nervous function of a high order. This is well illustrated by the exhaustive study by H. J. Berkley[9] after an examination of some two thousand five hundred slides. A summary of such a work hardly does it justice; I must therefore refer the reader to the original paper for details other than those that I will presently submit.

The outer layer of the organ was found by Luschka and Müller to be composed of gray matter similar to that found over the infundibulum. Berkley refers to this layer as composed of slightly irregular *ependymal* cells three or four deep, through which rather thick ball-tipped filaments penetrate to the second anatomical subdivision of the lobe. This outer coating of cells does not extend around the entire lobe, however, but covers only its free, or posterior, surface. Its anterior portion, that nearest the partition between the two lobes, has no such covering, so that its elements appear to be in contact with the partition itself or to be only separated from it by its capsule. The second subdivision of the posterior organ occupies, judging from Berkley's drawings, about one-third of its mass, and recalls, as to structure, that of the anterior lobe.

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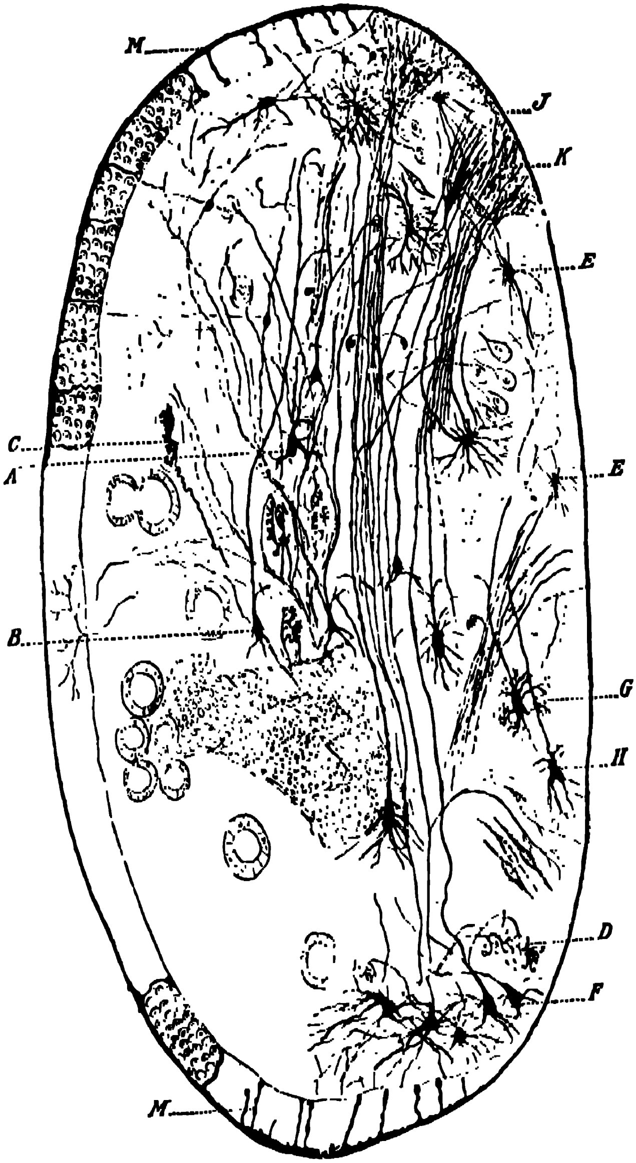
[8] Berkley: Brain, Winter, 1894.
[9] *Ibid.*



VERTICAL SECTION OF THE POSTERIOR PITUITARY BODY. [Berkley.]

Somewhat diagrammatic to indicate various types of cells. Its normal size is that of a small pea.

[*Brain.*]

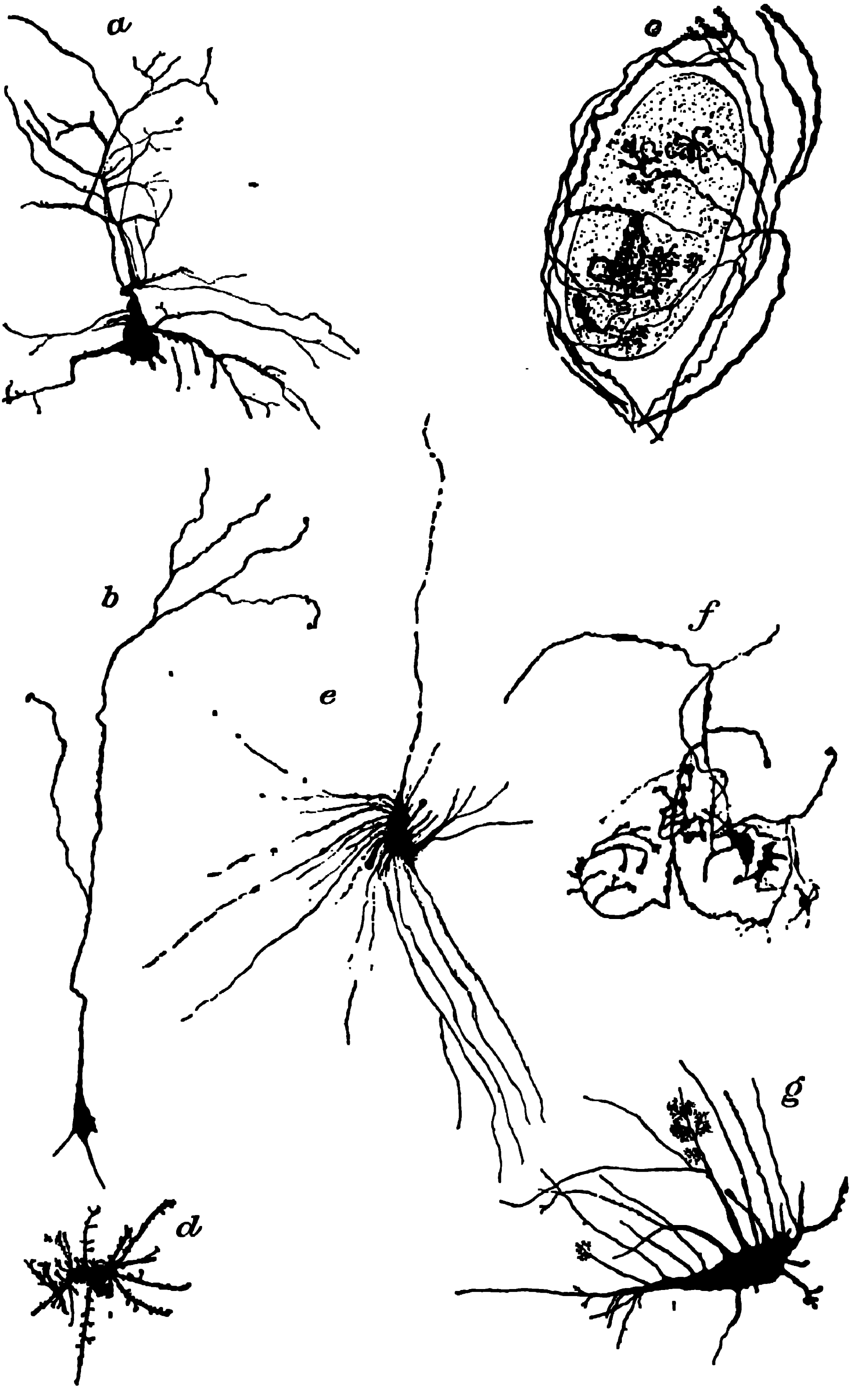
Again do we find the closed glands, or alveoli, including the colloid substance. Again are the glandular elements supported by connective-tissue trabeculæ permeated with capillaries, though the caliber of the larger vessels is somewhat smaller. Yet—a feature which seems to me important—the colloid alveoli are always most numerous near the outer edge of the ependymal cells, that portion farthest away from the interlobular partition, while the space between these structures and the partition is occupied by cellular elements of an entirely different kind.

The third portion may be said to occupy nearly two-thirds of the entire lobe: a perfect maze of nervous elements, some of which have not so far been found elsewhere in the organism. Yet connective-tissue partitions carrying blood-vessels are discernible throughout this entire area: a feature which suggests that an orderly subdivision exists. Its nervous elements vary greatly in form, but they may be divided into three general classes: 1. Cells that give off protoplasmic extensions, neuraxons, etc., that are not sufficiently long to reach the upper, anterior region of the lobe: *i.e.*, the infundibular region. 2. Cells the extensions of which reach this region. 3. Cells that are found mainly or only in this portion of the organ.

The *first class* includes flask-like cells with knot-tipped fibers that recall those of the anterior lobe (Fig. *A*, Plate I, and Fig. *a*, Plate II). These bodies are widely distributed, but their multitude of ramifications end freely among neighboring structures. Similar, though smaller, cells (Fig. *B*, Plate I, and Fig. *b*, Plate II) are found chiefly in the center, and have processes that extend upward a considerable distance and there often terminate in a brush-like figure. In this class may be included peculiar oval bodies (Fig. *C*, Plate I, and Fig. *c*, Plate II), mainly found in the center of the organ, that recall closed follicles. They give off axis-cylinders that coil about them irregularly, and fibers which terminate either in irregular figures resembling combs with knob-tipped teeth or in cat-o'-nine-tail-like tufts. Neuroglia cells, especially those of the mossy kind, are shown in Fig. *d*. Plate II, while spider-cells (Fig. *E*, Plate I, and Fig. *e*, Plate II) are mainly found where the nerve-cells are very numerous: *i.e.*, the anterior third of the lobe. The spider-cells, however, which only differ fror those found in the cerebral tissues by their larger size in pro portion to the length of their tentacles, outnumber the othe cells as the upper infundibular region of the lobe is reache

The cells included in the *second class* are all, as state distinguished by one or more protoplasmic extensions, whic insinuate themselves between all the elements intervening b tween their starting-point and the infundibular area referr to, where they break up into figures. The lowermost these, the ganglion-cells shown in Fig. *F*, Plate I, and Fig. Plate II, exemplify this type very well, since their extensio traverse the entire organ in an upward direction and end i the upper infundibular area. Higher up in the organ lar pyramidal and oval cells are found (Fig. *G*, Plate I; Fig. Plate II, and *g*, Plate III), the terminal subdivisions of whi break up into exceedingly fine feathery filaments. The on axis-cylinder of this cell, after distributing a few branches neighboring elements, continues upward and subdivides, wh near the upper margin of the infundibular region, into a co plex net-work which entwines the alveoli found there. A thi type, characterized by short dendrites and many hair-li processes (Fig. *H*, Plate I, and Fig. *h*, Plate III), is fou throughout the entire nervous area and also gives off one lo dendrite, which extends a long distance upward and forwar this extension may possibly reach the infundibular region its neighborhood. Coming from every direction, these lo dendrites seem, at any rate, to point all toward this one regio The other dendrites are short and distinguished by the pr ence of more or less numerous hairy processes, while some the terminal ramifications are ball-tipped—suggesting a p sible identity as collectors of energy, which, transformed in t body of the cell, are directed upward by the long dendrites.

In the infundibular region of the lobe—*i.e.*, the cellul elements of the *third class*—the final ramifications of the lo dendrites form an extremely complex aggregation of tuft figures, wavy threads, and feathery protoplasmic ramificatio In the midst of this maze of nervous elements certain cells a to be found, the like of which Berkley has not been able detect in any part of the central or peripheral nervous syste



VARIOUS TYPES OF CELLS IN THE POSTERIOR PITUITARY BODY. [Berkley.]

[*Brain.*]

They are small and round, and give off strong dendrites, which appear knotted or covered with thorns, giving them a "prickly appearance" (Fig. *J*, Plate I, and Fig. *j*, Plate III). Another variety found in abundance in this region is a small cell with a rich, apical tuft of fine, wavy processes. They are also distributed in the midst of a net-work of varicose nerve-fibers (Fig. *K*, Plate I, and Fig. *k*, Plate III) in the upper and near the anterior border of the lobe "along the space formerly occupied by the infundibular duct." As already stated, the spider-cell is to be found in great abundance in this locality, which, added to the other two varieties of cell, gives us three main cellular elements as representatives of the class of cells found mainly or only in the upper infundibular region of the organ.

As already stated, I do not regard it as a secreting structure. The view that it produces an internal secretion is merely assumed. Howell found that, while an extract of the anterior lobe produced no effect, an extract of the posterior lobe caused a rise of the blood-pressure. Since then, also, considerable use of such extracts has been made in therapeutics. But the facts that these effects correspond admittedly with those of adrenal extract, that they give the adrenal reaction, and that the presence in the organ of chromaffin cells has been established suggest that we are not dealing with a secretion. In fact, in practically all animals, excepting the cat and dog, there is no connection with the third ventricle above.

On the other hand, there is, we have seen, good ground for the belief that, as I pointed out in 1903, the posterior lobe is a general nerve-center, and that, through its nervous connection with the adrenals, it governs, besides, general oxygenation. That this view is gaining ground is shown by the recent statement of Lewin, of Berlin,[10] that "the majority hold that the hypophysis is a ductless gland that has an influence over the nervous system or has something to do with the red blood-corpuscles."

And, yet, what is the connecting structure between the posterior pituitary body and the parts to which, under such conditions, its energy would be supplied? Berkley believes—erroneously, we have seen—that none of the nervous elements of the infundibular lobe itself pass beyond its limits into the infundibulum. His histological work shows that, while "all the axis-cylinder processes and the long dendrites have a general tendency upward and forward, both dendrites and neuraxons branching as they proceed onward, all traces of the dendrites of the inferior and median cells of the lobe are lost some little distance below the superior edge." After an allusion to the vessels and fibrillated tissues that connect the infundibulum with the posterior lobe, he says: "The whole arrangement of the structures of the infundibulum" is "here altered." Then, referring to both lobes, *i.e.*, the hypophysis, he remarks: "Elsewhere it shows no break in the described arrangement, the line of differentiation between hypophysis and infundibulum being sharply drawn, a layer of coarse connective-tissue bundles being placed between and separating the glandular and other structures of the pituitary from the tissues of the infundibulum." While the neural lobe is autonomous, Ramon y Cajal, Andriezen, Gentès and others have conclusively shown, as previously stated, that nerve-fibers passed from this lobe and the *pars intermedia* to the tuber cinereum and beyond.

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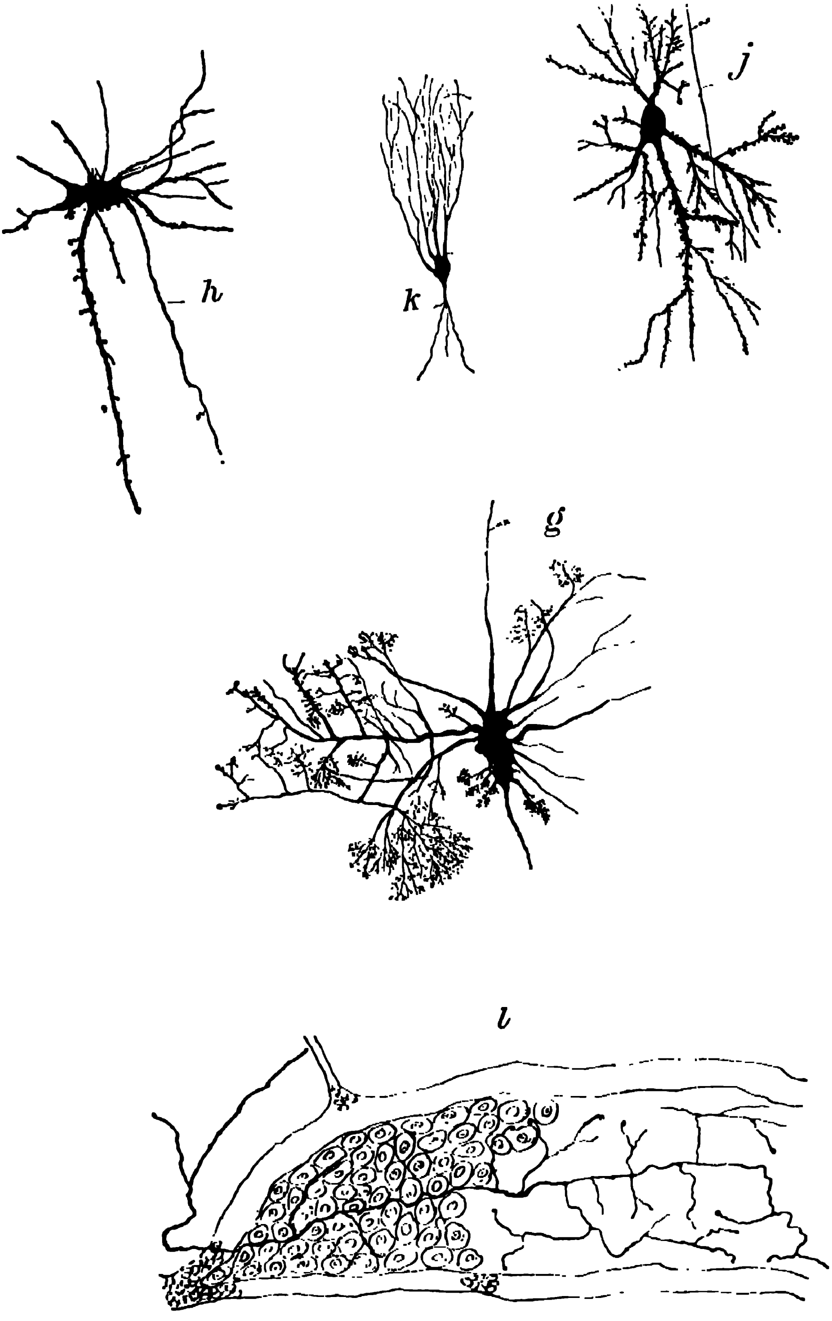
[10] Lewin: quoted by Archibald Church, Journal Am. Med. Assoc., July 10, 1909.

Notwithstanding this striking autonomy of the organ, there are several features in its histological make-up that suggest an additional connecting-link between it and the infundibular structures. Berkley refers to the "outer lamina of slightly irregular ependymal cells (Fig. *M*, Plate I) three or four deep, arranged after the manner of the *cuticular epithelium.*" This lamina, which older anatomists considered as a continuation of the ventricular gray substance, only covers, we have seen, the free portion of the posterior lobe and is not continuous with the infundibular ependyma. Again, "there are seen, extending from the thin capsule surrounding it" (here Berkley alludes to the *capsule* that surrounds the entire posterior lobe), "numbers of rather thick varicose threads, all unbranched, and invariably ending, when their terminations can be discovered, in a ball-shaped figure, at a definite line in the substance of the body, usually at the *inward* ending of the first layer of epithelial cells, at the line of separation from the more centrally situated elements. These knobby threads," he says, "strongly resemble the ependymal glia-cells of embryonic life, and possibly may be related to them; but, as their



VARIOUS TYPES OF CELLS IN THE ANTERIOR AND POSTERIOR PITUITARY BODIES. [Berkley.]

Figs. h, j, k, and g: Cells in the Posterior Pituitary Body. Fig. l: Portion of Glandular Elements of the Anterior Pituitary Body.

[*Brain.*]

basal end is shrouded in a blackened aggregation of cellular masses, their histological origin must remain a matter of some uncertainty."

If, with these histological data before us, we examine Plate I, a suggestive fact asserts itself: *i.e.*, that the lamina of ependymal cells referred to forms a skull-cap-like covering for the posterior two-thirds of the posterior lobe. The glandular alveoli of the latter, with their colloid substance, are, therefore, in the best possible position for the reception of any nervous impulse that the ependymal cells may be able to transmit outwardly. This is emphasized in Plate I, which shows that this layer exactly covers the entire surface of the posterior region without reaching beyond its limits. The posterior surface of the posterior lobe thus seems to be held in the grasp, as it were, of its ependymal covering, which in turn contains the nervous, "rather thick, varicose threads." This suggests that the capsule may not be the insignificant structure it is now thought to be. Even the fragmentary data we have concerning it tend to indicate that it plays an important rôle in the functions of the organ.

Mere protective structures are usually detached without much difficulty from the underlying tissues. Berkley states, referring to the posterior body: "This lobe is so strongly adherent to the dura that it pulls out of the rest of the pituitary body in removing this with the brain, unless the membrane is dissected with it from the base of the skull." Since the capsule is the part of the lobe so strongly connected with the dura, it must as firmly adhere to the layer of ependymal cells beneath; otherwise efforts at removal would tear it away from the latter. This firm hold of the capsule on the cellular layer is fully accounted for by the thin, fibrous partitions the former sends through the latter, but this in itself suggests an intimate relationship between capsule and cellular layer, especially since the "blackened aggregation of cellular masses," referred to by Berkley, which form the basal extremities of the nervous "threads," all terminate in what appears to be, in his drawings, thickenings in the capsule proper. That such a relationship between the capsule and the nervous elements must exist is further shown by his reference, in the descriptive text of the illustration, to the "capsule of the lobe thickened in places, *from which* extend threads that end in knobs," etc. That the varicose threads and the capsule are structurally continuous, the latter thus dipping, through a multitude of protoplasmic projections, into the deeper elements of the lobe is evident.

We have seen that many features suggest a relationship between the *anterior* pituitary and the adrenals, through nerves at present considered as appurtenances of the sympathetic system. That the anterior lobe contains but one kind of nerve connected with this function—besides its vasoconstrictors—is shown by the following statement of Berkley's: "In the glandular portion of the body, nerves, other than those belonging to the sympathetic system, are not found. They are very fine *varicose* fibers, with numerous ramifications and branchlets coming off from the main stems at a right or slightly obtuse angle." These fibers must, therefore, represent, considering their general morphology and location, not terminals of the connecting nerves and distributors of energy, but *collectors* of energy, *i.e.*, of sensory impulses. They are probably the fibers which Cajal traced to the floor of the third ventricle. If Fig. *l* in Plate III, which represents a section of the glandular portion of the anterior lobe, is consulted, it will be seen that these nerves present the two main characteristics of the capsular threads of the posterior lobe: *i.e.*, they are also varicose and their tips are likewise knobbed. Since, therefore, the nerves so disposed in the anterior pituitary are collectors of energy, *the varicose and knobbed threads of the capsules of the posterior pituitary must also be collectors of energy.* This is further sustained by the analogy between the two organs to which reference has already been made.

That a direct nervous connection between the posterior pituitary and the infundibular tissues, etc., exists by way of the capsule of the former is thus probable—thus making it possible for impulses generated in the depths of the lobe to reach the ventricular structures, irrespective of the sharply defined connective-tissue separation between the lobe proper and the infundibulum. Indeed, such a separation seems a necessity, inasmuch as an impulse, transmitted through the intermediary of the capsule must, owing to the skull-cap shape of the latter, come from every part of the underlying structures and only reach the basal structures through paths that are continuous with the capsule's tissues, and irrespective of the nerves which arise directly from the two lobes and pass upward by way of the interior of the infundibulum. That a profuse padding of cellular tissue is Nature's resource under such conditions is well illustrated by the following remark of Déjerine's: "The vessels of the central nervous system are surrounded by two sheaths of a different kind: the *internal* is connective in nature and belongs to the mesodermic layer; the *external*, neurogliar in nature, is developed at the expense of the external, or ectodermic, layer." The capsule has been compared to the cerebral cortex, perhaps with justice, as we shall show.

Berkley, referring to the various cellular structures in the deeper portion of the lobe supplied with long extensions, says: "The axis-cylinder extensions of all the cells in the inferior portion of the lobe turn upward. . . . Those belonging to the larger proportion of the smaller cells of the superior border turn upward and intermingle with the marginal fiber net-work. . . . All the axis-cylinder processes and the long dendrites have a general tendency upward and forward, both dendrites and neuraxons branching as they proceed onward: but all traces of the dendrites of the inferior and median cells of the lobe are lost some little distance below the superior edge, and then the neurons only are intermingled with the extensions of the smaller superficial cells, passing them, however, before the border is finally reached, where they spread out into a most extensive fret-work of fine *varicose* fibers, still retaining something of their previous longitudinal arrangement from the threads of the uptending fibers being coarser than the lateral and intermingling branches. It is doubtful whether any of these fibers pass beyond the limit of the lobe into the infundibulum; our sections give no evidence of such an arrangement." This upward tendency of all cells, and the evident concentration of their functional activity at the upper extremity, seem to us to further emphasize the identity of the posterior lobe as a powerful source of energy. Its junction with the end of the infundibulum becomes, under these circumstances, the normal pathway for all the energy that the organ can accumulate. Capsule and protoplasmic extensions or processes all serve a similar purpose, but the neck of the organ is its own functional limit.

We must not lose sight of the fact, however, that other nerves penetrate the organ. This is shown by the fact that Berkley says, in this connection: "the nerve-fibers accompanying the larger arteries are sometimes distinctly seen coming from the infundibular tract into the body of the posterior lobe of the gland and ramifying through it." That there is no connection between these and the nervous structures previously described, however, is shown by the additional statement: "Connections between the fibers of the vascular supply and the nerve-cells of the organ we have never been able to observe. That these are the nerves through which the organ receives its own functional energy—*i.e.*, the impulses to its vessels and alveoli,—as in the case of other organs, is probable."

The prevailing view that the embryonal supporting substance of the brain and spinal cord, the ependymal neuroglia, almost entirely atrophies and disappears in the adult mammal would tend to counteract my belief that the capsule and its underlying structures are important factors of the posterior lobe's functions. Berkley, alluding to the writings of various observers in this connection, and referring to the infundibulum and other tissues of the third ventricle which he had just described, says: "After reading these statements, it was something of a surprise to find the above-described beautiful specimens of several types of ependymal neuroglia extending from *all portions of the middle and inferior regions of the cavity of the third ventricle* and reaching to the periphery, all portions, bodies, branches, tentacles, and subpial endings being readily distinguishable. The region examined is, therefore, very interesting not only from the great variety of neuroglia-cells that may be seen within a very limited area, but from the fact that varieties of the ependymal neuroglia-cells, *previously supposed to have entirely disappeared* from the central nervous system *in the adult* mammal, are found present in perfect condition in the brain of a very high order of animal, and *are not confined, as has previously been supposed, to those of adult reptiles, amphibia, and fishes.*"

If all the data I have submitted are considered collectively, it seems to me that the following conclusion is warranted: *Removal of the hemispheres in an animal does not arrest its power to execute normal bodily movements under external stimulation, because these movements are dependent upon functional structures situated in the base of the brain and in the spinal cord and which the posterior pituitary probably governs.*

Of course, this appears to contradict at once a great mass of experimental and clinical testimony, but the contradiction is only apparent. Removal of the motor areas in the rabbit gives rise to no detectable differences in the movements; the injured animal is similar to an intact one. In the dog, the same procedure, according to Foster, causes "loss or diminution of *voluntary* movement in the corresponding part of the body"; but this is only temporary, and the animal may recover to such a degree that the temporarily paralyzed limb cannot be told from the normal one. Careful examination of the brain after death shows that no regeneration of the lost part had occurred. Even removal of the whole motor area causes no appreciable difference between the movements of the two sides of the body to a casual observer. In the monkey the results have been unequal: "While in some instances recovery of the movement has, in the monkey, as in the dog, after awhile taken place, in other instances the 'paralysis' has appeared to be permanent." . . . "The facts, however, within our knowledge relating to the permanence of the effect are neither numerous nor exact enough to justify at present a definite conclusion," as stated by Foster. "On the other hand, the positive cases, where recovery has taken place, are of more value than the negative ones, since in the latter the recovery may have been hindered by concomitant events of a nature which we may call accidental." I might add that a single case of recovery in the monkey, when the motor area has been completely removed, demonstrates that, generally speaking, the structures are functionally similar in all higher animals, including man, judging from such instances as the crow-bar case, or one reported by Brown-Séquard,[11] in which 'an entire lobe was destroyed and in which the only symptoms were amaurosis and slight headache. This emphasizes the identity of the cerebral hemispheres as an aggregate of centers which record impressions and are the seat of reason, intelligence, and volition, but it also suggests that the word "motor" is only applicable in its literal sense to the areas in the lower cerebral mechanism: *i.e.*, the intermediary through which the mandates from the hemispheres are executed.

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[11] Brown-Séquard: Société de Biologie, 1876.

I have previously referred to the misleading information afforded by the use of electrical stimulation. Nowhere in the organism does this seem to be more applicable than to the brain. This feature and the complexity of the processes involved are fully emphasized in the following lines of the late Dr. Foster: "Some writers appear to entertain the conception that in a voluntary movement, such as that of the forelimb, all that takes place is that the 'will' stimulates certain cells in the cortical area, causing the discharge of motor impulses along the pyramidal fibers connected with those cells, and that these motor impulses travel straight down the pyramidal tract to the motor fibers of the appropriate nerves, undergoing possibly some change at the place in the cord where the pyramidal fiber makes junction with the fiber of the anterior root, but deriving their chief, if not their whole, co-ordination from the cortex itself: that is to say, being co-ordinated at their starting-point. That such a view is untenable and that the simplicity of the electrical phenomena is misleading are shown by the following two considerations, among others: On the one hand, as was shown in a previous section, the co-ordination of movements may be carried out apart from the cortex, namely: in the absence of the hemispheres; and we can hardly suppose that there should be two quite distinct systems of co-ordination to carry out the same movement: one employed when volition was the moving cause, and the other when something else led to the movement. On the other hand, the analogy of speech justifies us in concluding that the cortical processes do take advantage of co-ordination effected by the action of other parts of the nervous system."

Referring directly to the general character of the processes involved, Professor Foster says: "Hence, while admitting, as we must do, that in the intact animal the cortical area and pyramidal tract play their part in carrying out voluntary movements, their action is not of that simple character supposed by the view referred to above. On the contrary, we are driven to regard them rather as links—important links, it is true, but still links—in a complex chain. As we have already urged, we may probably speak of the changes taking place in the pyramidal fibers as being, on the whole, of the nature of efferent impulses; but *we would go beyond the evidence if we concluded that they were identical with the ordinary efferent impulses of motor nerves.*"[12] All the features emphasized in these quotations, especially in the last lines, appear to me to isolate the hemispheres from the *source* of motor impulses *per se,* and to confirm what experimental evidence obtained after removal of the hemispheres had suggested: *i.e.,* that the *lower* cerebro-spinal structures constitute the executive intermediary through which the cortical mandates are actively realized. Yet, as is well known, these lower structures, in turn, manifest their activity through the centers imbedded in them; what is there to replace the energy in the form of motor impulses which is erroneously supposed to be awakened by the "will" in "certain cells of the cortical area"?

Professor Foster partially answers this question when he says: "The discussion in a previous section has shown that much of the co-ordination of the body is carried out by the *middle portions of the brain,* and on these the motor area must have its hold as on the spinal mechanisms. The details of the nature of that hold are at present unknown to us." It would appear from the facts reviewed that what might be termed the *central* brain and the spinal cord constitute an entity—a mechanical entity, perhaps—made up of working centers, beginning with the olfactory bulb and the other nervous structures distributed to the nasal mucous membrane anteriorly, and terminating with the end of the spinal cord: *i.e.,* the neural tract of lower forms. Motility, unconscious co-ordination, and sensation—but only, in the case of the latter, to the extent of *transmitting* sensory impressions to their respective perception-centers—would enter within the scope of this central brain.

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[12] The italics are my own.

As to the source of the transmitted energy or impulses,—apart from the sensory connections with underlying structures which the cortex possesses,—the predilection of most writers to ascribe to the cortical areas motor functions but demonstrates the need of such an agency to logically account for the phenomena witnessed. To ascribe to the central brain or its centers *per se* attributes of a similar kind would simply amount to shifting to it a convenient, but unknown, quantity, and a fictitious one besides, in the sense that it supplies nothing to account for something. In the only nervous system that I have so far traced to its origin, that of the suprarenal glands, the conversion of chemical energy into nervous impulses was found to be a functional attribute of the anterior pituitary body. That so extensive a system as that represented by the central brain and cord should likewise need a center such as that represented by the posterior pituitary body for the conversion of some form of energy of external source to satisfy the needs not only of its efferent, but also its afferent, impulses seems clear.

That the middle brain is the source of the motor phenomena witnessed is not only suggested by the fact that normal muscular contractility promptly recurs after removal of the hemispheres, but also by the following experiment by Professor M. Duval: "If a part of the gray substance of the cortex designated as the center of certain movements is cauterized, the same movements are obtained when the electrodes are applied upon the eschar thus produced. . . . This experiment shows," says the author, "that the gray cortical substance is not a necessary experimental condition for the production of localized movements." Indeed, he states that the underlying white substance of certain parts will also cause circumscribed motions in certain groups of muscles, etc.

Can the removal of the cortex of one side be followed by the assumption of compensative functions by the opposite side? After the usual period of paralysis, due to shock, the normal motions promptly recurred, precisely as they had on the other side. To ascertain whether the cortex at all possessed motor attributes Vulpian passed an electrode through it, that part in contact with the cortex being insulated. The underlying white substance was thus alone stimulated. He found that the latter was far more easily excited than the cortex. It seems clear that in these experiments *the increased excitability was due to the closer proximity of the central brain.* "All the functions of the brain can persist," says Brown-Séquard, "after the complete destruction of an entire lobe."[13] Experimental and clinical evidence, however, only eliminate motility and co-ordination from the hemispheres. The cortex, as regards cerebral localization, merely loses the "motor" attribute suggested by the term "motor area," and is shown, by its functional relations with the underlying structures, to be a vast sensitive surface, to the "areas" of which the term "sensory" might be more fittingly applied.

The practical bearing of this may be illustrated by an experiment that will recall some of the familiar features of the earlier portions of this work and at the same time point to the central brain as the source of motor phenomena. This experiment, referred to by Professor Foster, is as follows: "It has been observed that in certain stages of the influence of morphine the cortex and the rest of the nervous system are in such a condition that the application of even a momentary stimulus to an area leads not to a simple movement, but to a long-continued tonic contraction of the appropriate muscles." As previously shown, many drugs raise the blood-pressure and thus congest the adrenals and indirectly the brain. Cerebral hyperæmia, we have seen, is the source of the majority of phenomena that follow the ingestion of drugs that are sufficiently active to stimulate the adrenals. The intense headache of quinine and other agents is obviously due to this congestion of the cerebral vessels; muscular contractions, tetany, etc., are also familiar results of suprarenal overactivity; indeed, digitalis, one of the most active suprarenal stimulants, is particularly active in predisposing muscles to contraction and in experimental animals suitably dosed a minimal current without the drug will produce maximum effects—prolonged tetany—with it.

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[13] M. Duval: *Loc. cit.*, p. 115.

In the course of the statements to which I have referred, Foster, after ascribing the temporary paralysis observed after operative interference to a condition "of the nature of shock," remarks: "But, even giving full weight to this consideration, there remains the fact that the cortical area is *associated* with various co-ordinating and other nervous mechanisms belonging to the limbs by such close ties that these are thrown into disorder when it is injured. And, side by side with this, we may put the remarkable fact, previously stated, that during an *abnormal* condition of the cortical area—simulation of the area—instead of producing the appropriate movements confined to the limb may give rise to movements of other parts *culminating in epileptiform convulsions.*"[14]

If the word "associated" is given its full meaning, limbs and co-ordinating mechanism constituting one class, and the cortical surface the other, *the hemispherical mantle of gray matter being considered solely as a great sensory surface,* the demands of experimental evidence seem to me to be satisfied. What are epileptic convulsions after all but manifestations of excessive *motor* activity? . . . Can the latter be credited to the cerebral cortex, as is now taught in text-books? Obviously not, since experimental evidence proves that the cortex has no motor properties *per se.* But irritation of this sensory surface or an accumulation of physiological toxics, which periodically becomes sufficiently great to so stimulate the vasomotor center as to cause violent hyperæmia, not only of the sensory cortex, but also of its executive mechanism, the middle brain, are the clearly defined causes to which physiological and chemical evidence points. Could the cortex without the middle brain give rise to the same phenomena? That such is not the case is shown by the preservation of all motor functions, including co-ordination, after removal of the hemispheres. Indeed, it is only when the middle brain is removed that the experimental animal thus deprived of its sentient cortex and of its dynamic center practically loses its identity as a living thing. Hence it seems clear that *the motor phenomena caused*

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[14] All italics are my own.

by stimulation of the motor areas of the cortex are manifestations of activity of the central gray matter at the base of the brain, incited therein by sensory impulses from these cortical areas.

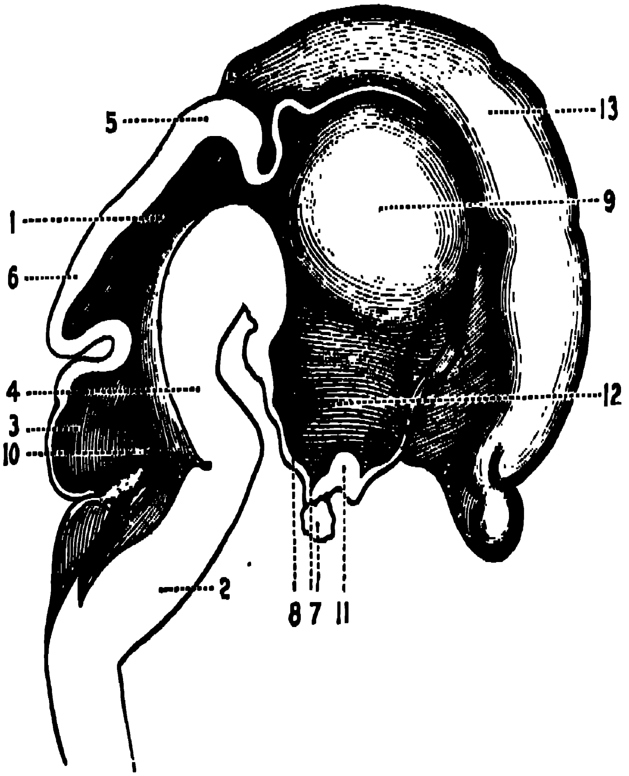
What constitutes this lower brain? The co-ordination, so evidently preserved in animals deprived of their hemispheres, points to the cerebellum as a possible member of the group of organs to be considered in this connection. Including this organ, therefore, and beginning with the anterior structures, we would now have: the posterior pituitary body; the infundibulum; the central gray matter, forming "a bed for the development of the nuclei of the cranial nerves"; the tegmental system,—*i.e.*, the reticular formation in the medulla continued to the subthalamic region, and to which belong the red nucleus and other bulbar nuclei. All this forms what Foster so aptly characterizes as "a more or less continuous column of gray matter" connected with the spinal cord by various ties, besides being, as it were, "a continuation of the spinal gray matter." It is as evident that the optic thalami and corpora quadrigemina are also members of the group, since these related organs appear to be necessary for the success of the experiment in which both cerebral hemispheres are removed. Thus, referring to the frog, Foster says: "In this animal it is comparatively easy to remove the cerebral hemispheres, including the parts corresponding to the corpora striata, leaving behind, intact and uninjured, the *optic thalami* with the optic lobes, the representatives of the *corpora quadrigemina,* the small cerebellum, and the bulb. If the animal be carefully fed and attended to, it may be kept alive for a very long time: for more than a year, for instance."

If, with this list before us, we now examine the annexed illustration, originally from His's work, and, therefore, not recently drawn, a rather suggestive coincidence appears, indicating, perhaps, a total independence, in the embryo, of the region containing all the structures enumerated from the vesicle which subsequently develops into the hemisphere of the same side. In mammals the latter is at first insignificant, but it develops very rapidly, soon overlapping the middle structures. The outline of the latter is colored bluish gray. The name of each part is given on the cut: a feature that will better convey the mutual relations of the various structures included in this system than a verbal description.

Again, the location of the posterior pituitary at the very head of the entire spinal system, as shown in the illustration, adds further testimony to that already submitted to demonstrate the functional relationship between the nervous structures lying in the posterior pituitary, including the floor of the fourth ventricle, and the bulb.

A summary of all these facts, *i.e.*, (1) that the posterior pituitary body has a phylogenetic history which distinctly identifies it as a part of the entire neural tract; (2) that it presents clearly defined histological characteristics of an active neural organ; (3) that these characteristics extend to the infundibulum, the tuber cinereum, the floor and sides of the third ventricle; (4) that these structures are continuous with the reticular substance of the tegmental region, the medulla, and the cord; (5) that the posterior pituitary body has been found to be in direct relation with the olfatory center and the bulbo-spinal axis in all classes of vertebrates; (6) that a current passed between the olfactory and medullar centers may cause heart-inhibition and death; (7) that various nerve-centers are included in the structures with which the pituitary is functionally connected in all vertebrates; (8) that sudden death is caused by a puncture in the region of the vagal bulbar center through interruption of the efferent and afferent impulses through which the cardio-pulmonary system is incited to activity and governed; (9) that electrical excitation of the exposed pituitary body causes an instantaneous rise of the blood-pressure of over 100 mm. Hg.; (10) that removal of the pituitary causes the opposite, *i.e.*, an immediate and great fall of the blood-pressure; (11) that division of the base of the brain across the path of nerves known to originate in the pituitary body prevents the action of drugs, such as antipyrin, which lower the temperature, and also the action of pus and other septic materials which cause fever; and finally (12) that all functions carried on normally after removal of the brain are caused to cease by removal of the pituitary, seems to me to warrant the conclusion that:—

The posterior pituitary body is the chief center of the spi-



MEDIAN AND VERTICAL SECTION OF A TWO AND ONE-HALF MONTHS' EMBRYO. (His.)

[Considerably Enlarged.]

1, Aqueduct of Sylvius. 2, Medulla Oblongata. 3, Cerebellum. 4, Pons Varolii. 5, Anterior Tubercula Quadrigemina. 6, Posterior Tubercula Quadrigemina. 7, Infundibulum and Pituitary Bodies. 8, Tuber Cinereum. 9, Optic Thalamus. 10, Fourth Ventricle. 11, Hypoglossal Nerve [Twelfth Pair]. 12, Third Ventricle. 13, Hemisphere Vesicle.

nal system, and, as such the primary source of certain excito-motor impulses now believed to arise in the bulb.

Of course this conception conflicts with the prevailing view that the pituitary body is the source of an internal secretion; but there is ground for the belief that some leading investigators are not convinced of the existence of the latter. Swale Vincent, we have seen, finds it "extremely difficult to imagine how such a structure," referring to the posterior lobe, "can be regarded as a secreting gland." In an analytical paper, E. A. Schäfer,[15] though a partisan of the secretion theory, concedes that "some functions of the organ might be conceived to be carried out through the agency of nerves." Nothing so far published has, in my opinion, raised the secretion theory beyond the level of a plausible assumption. (See also page 173 in the present volume.)

If, however, the posterior pituitary holds the important relation to the nervous system I believe it does, its influence in the pathogenesis of general neuroses must be very great. No disease having so far been associated with the *posterior* lobe, it may prove profitable to seek among the symptoms of typical disease of the *anterior* lobe what signs might be assigned to implication of the posterior, with which it is intimately blended.

Acromegaly, which may be attended by irregularity of the reflexes, paræsthesias, localized pains, vasomotor neuroses, paraplegia, etc., and known to be due solely to lesions of the pituitary, suggests itself as a profitable field of study in this connection.

It is interesting to note, in this connection, that quite a number of exceptionally able clinicians—von Recklinghausen, for instance—have considered acromegaly as a trophic neurosis, the organic disease of the pituitary being deemed secondary. That the various theories adduced also bear upon *nutrition* of the nervous elements is significant as testimony in favor of my view. Indeed, the clinical signs that point to impaired nervous action are numerous, and are present in practically all cases of acromegaly when the anterior lobe has become sufficiently enlarged or functionally disordered to involve the posterior lobe, either directly by pressure, continuity of tissue, etc., or indirectly by overstimulating the adrenals, or, in the later stages, by causing insufficiency of these organs.

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[15] **Schäfer: Proceedings of the Royal Society of Medicine, May, 1913.**

In a previous chapter I have, on good grounds, I believe, ascribed to overactivity of the adrenals the stage of "erethism," and to insufficiency of these glands that of "cachexia." But, if we ask *how* these states are produced by the adrenals, the answer which would not have been available before now seems to be within our reach.

I have previously referred to the vicious circle that obtains in acromegaly. Though primarily located in the anterior pituitary, the lesion probably gives rise to no untoward symptom until well advanced: *i.e.,* until pressure occurs either upon its own structure by the pathological elements or upon the posterior pituitary. Even slight pressure upon the whole organ, as shown by de Cyon,[16] gives rise to marked general symptoms. But if the posterior pituitary is also considered as a factor in the production of the symptomatic phenomena, as a source of nervous energy, we not only have the vascular erethism of suprarenal overactivity, but distinct evidence of *nervous* erethism besides. This is well illustrated by the following *quoted* lines, *i.e.,* Gauthier's definition of the erethic stage of acromegaly as given by Hinsdale[17]: "The phenomena of *erethism* which characterizes the *first stage* embraces, first, a painful *hyperæsthesia,* which manifests itself in headaches and rheumatic pains; second, an hypertrophy of the muscular fibers which may give to patients a muscular power greater than usual; third, palpitation of the heart accompanying the hypertrophy of that organ; and, finally, the polyphagia and polyuria which may be considered to be connected with an erethic state of the respective organs." Everything here points to overactivity. But these are only the milder manifestations. Tamburini, for instance, describes a case in which "the mental symptoms, on account of which the patient was sent to the asylum, began to show themselves only a year before her admission. They consisted chiefly in delusions of suspicion accompanied by threats and acts of violence. The patient presented, in a marked degree, the bodily changes characteristic of acromegaly. While in the asylum she was confused, resistive, and suicidal, and refused her food. . . . Only the anterior lobe was involved, the posterior presenting no change either in volume or structure." This typifies the irritability or stimulation induced by pressure without organic change.

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[16] De Cyon: Archives de Physiologie, July, 1898.

[17] Hinsdale: *Loc. cit.,* p. 30.

The phenomena produced are of another kind when both organs are involved in the morbid process, as appears to be the case in the following instance reported by Johnston and Monro[18]: The patient, a woman, "was taciturn and intellectually obtuse, and her memory was bad. Her utterance was thick and indistinct, as if her tongue were too big for her mouth. Her gait was slow and shuffling; her expression partly melancholic, partly demented. . . . The skin of the face is of a dull-yellowish tint; the mucous surfaces are pale. . . . Hearing is somewhat impaired. Reflexes are diminished. The subject of these notes remained in hospital for about four weeks. She scarcely ever spoke, took no interest in anything, and slept about sixteen hours daily. . . . She was readmitted in September—blind, more deaf, more drowsy, very feeble in muscular power. She could no longer rise without assistance. Control over the sphincters was lost. . . . Paralyzed. For a couple of months before death there was a discharge of clear fluid from the nose. . . . The pituitary body is represented by a large, red mass, almost diffluent—much softer than brain-substance." The entire organ being destroyed, the posterior lobe had obviously followed the fate of its mate.

In a case described by Pirie[19] the history of the nervous symptoms is very clearly defined, though the author was unfortunately unable to obtain an autopsy. "The disease first manifested itself in 1886, when menstruation finally ceased. Pains and paræsthesia of the arms and legs were felt, and the patient noticed that her hands and feet were getting larger and more awkward. . . . Along with the development of physical symptoms a peculiar alteration of mental condition took place. Attacks of narcolepsy overcame her, she became sluggish and irritable, and she suffered much from the *ennui* of life. . . . Breathlessness on the slightest exertion appeared, and ultimately the muscle weariness so gained upon her that she had to take entirely to bed. . . . Sensory disturbances are marked. Shooting pains in combination with paræsthesia, tingling, and numbness are complained of in the arms and legs. Neuralgic pains are felt also in various parts of the body, viz.: the face, chest, back and loins. A remarkable perversion of thermic sensibility is found in the lower limbs and over the front of the abdomen and chest up to about the level of the fourth rib, the patient having no sensation of heat in these regions. . . . Sternberg remarks particularly on the occurrence of pain and paræsthesia as valuable signs for diagnosis in the early stages of the disease; they are probably due, he considers, to changes in the cutaneous nerves."

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[18] Johnston and Monro: Glasgow Medical Journal, August, 1898.

[19] Pirie: London Lancet, Oct. 5, 1901.

In a previous chapter I remarked: "Whether the mental symptoms are ascribable to the cerebral hyperæmia or to the impairment of certain functions of the pituitary itself, or to both, it is as yet impossible to say." It now seems evident that *both* organs are involved in the pathogenic process. If the far-reaching meaning of this fact is apprehended, it seems clear that there lies hidden under the whole fabric—of which we only now see the outline—a truth of overwhelming importance to us physicians: *i.e.*, the fact that *it is not alone in acromegaly that the typical signs of impaired function of the posterior pituitary appear, but in other syndromes directly ascribable to the adrenal system: i.e., myxœdema, cretinism, exophthalmic goiter, and Addison's disease, which include in their aggregate the majority of organic changes of a morbid kind to which the system is liable, besides nervous phenomena.*

This may be briefly illustrated by further quotations from Dr. Pirie's excellent paper, entirely devoted to the one case. As regards the *muscular system,* the author states that "muscular atrophy is a prominent feature, affecting the thenar, hypothenar, and interossei muscles of the hands, the forearm- and arm-muscles, the calf- and thigh-muscles, and also the glutei," and refers to Duchesnau,[20] "who has made a special study of the atrophy of muscles in acromegaly. So marked is it in some cases that it has been mistaken for syringomyelia, progressive muscular atrophy, or amyotrophic lateral sclerosis; it has also been mistaken for Charcot's cervical pachymeningitis hypertrophica and for erythromelalgia." Referring to the *skin,* Pirie says: "Its chromatogenous functions are disturbed, much as in rheumatoid arthritis. Small freckles are frequent; patches of a yellowish bronzing occur also on the face, the chest, and the insides of the thighs. (Motais describes a bronzing such as occurs in Addison's disease.) Numerous small warts are present. (Mollusca fibrosa are described in many cases and xanthoma-like tumors by Dallemagne.) The patient suffers from a brownish seborrhœa, especially troublesome in the scalp. The hair is thick and coarse and stands straight upward. There is a scanty beard and moustache. Profuse perspirations are constantly complained of. The heart is dilated. There is tachycardia, the heart beating about 98 to the minute. A soft, systolic, basic murmur is heard at times. Palpitations and fainting fits occur very often. Dyspnœa is marked, and asthmatic-like attacks occur, during which the patient has to sit up in bed and fight for her breath." . . . "The *soft parts* are remarkably changed as well *as the bones.* The scalp is much thickened, as is also the skin of the face. . . . In addition to the kyphosis there is a compensatory lumbar lordosis and also a certain degree of scoliosis. The clavicles are enormously hypertrophied. The ribs are thickened and expanded, the costal cartilages feel bony, and there are nodular projections resembling the 'rachitic chaplet' at the junctions of the ribs and their cartilages." . . . "With regard to the *organs of special senses,* the skin of the eyelids is thickened and puffy. The lacrymal glands are hypertrophied. Increased lacrymation occurs at times, and I have noticed a colloid-like secretion between the eyelids." . . . "There is amblyopia, nearly complete in the left eye, and color-vision for blues and yellows is defective. Bitemporal hemianopsia is present. The pupils contract in accommodation and react to light, though very sluggishly in the case of the left eye. With the ophthalmoscope optic atrophy is found." . . . "She suffered much at this time from polydipsia and *glycosuria,* and for over twelve months there was an almost constant dribbling of saliva from the mouth. . . . The thyroid was greatly enlarged, but under treatment with thyroid substance it diminished much in size." We have seen how dependent the organism is upon the integrity of the suprarenal system when infectious diseases develop.

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[20] Duchesnau: Thèse de Lyon, 1891.

I can fully agree with Harlow Brooks[21] when he says: "It is quite natural to expect pronounced abnormalities in the various portions of the nervous system in a disease which exhibits so many neurological symptoms"; and his statement that "examinations of the nerve-tissues have shown quite *extensive* and *general* changes" further sustains my deductions. Evidence of this kind, garnered from all sides long before the feature it serves to support is thought of, appears to me of the strongest kind. I again prefer to use the author's own words, therefore, rather than my own, when he reviews the pathology of the disease, and which seems to me to portray *in parvo* the main landmarks of neurological pathology. I have only omitted those of the author's own estimates that do not bear directly upon my subject and what text was not purely descriptive:—

"*Peripheral Nerves.*—The trunks of the peripheral nerves are, for the most part, enlarged; this is directly due to an increase in the connective tissue of the endoneurium and perineurium. Often the sheaths of the nerve-trunks also show considerable thickening. This general connective-tissue hyperplasia frequently so encroaches on the nerve-fibers as to destroy them, and degenerated nerve-fibers are quite commonly found some of which may show complete axis-cylinder destruction (Arnold, Comini). These conditions may persist throughout the entire nerve-trunk, extending even into the nerve-roots. (Arnold, Duchesneau.)

"*Ganglia.*—In the posterior-root ganglia, also, we find the connective-tissue elements greatly increased, so that even macroscopically the ganglia are often considerably enlarged. Microscopically the ganglionic cells are sometimes pressed upon and atrophied (Marie, Marinesco). Arnold reports that he found vacuoles in the nerve-cells. In Cases I and II of the author's, the alterations in the ganglion-cells were slight.

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[21] Harlow Brooks: Archives of Neurology and Psychopathology, vol. 1, No. 4, 1898, p. 592.

"It is difficult to determine whether the nerve-cell lesions are secondary, perhaps directly dependent on the connective-tissue hyperplasia about the cells and fibers, or are primarily due to defective nutrition of the ganglion-cell bodies. Perhaps these ganglionic changes are wholly, or in greater part, responsible for the degenerations and atrophies which take place in the muscles of the voluntary system.

"*Sympathetic Ganglia.*—The changes in the sympathetic ganglia and trunks have been made the subject of special study by several very prominent investigators, among whom are Marie, Marinesco, and Arnold, and have been looked upon by many as factors of an etiological nature. Finding, as we do, such pronounced change in the blood-vessels, it does not seem at all strange that lesions in the sympathetic ganglia should be present; but a view intimating a dependence or relation of the vascular changes to the lesions in the sympathetic system is not in accordance with our own ideas expressed at the close of this paragraph. In general, the changes in the sympathetic ganglia are very similar to those already described in the ganglia and trunks of the cerebro-spinal system. In some cases the size of the ganglia is considerably increased (Arnold, Marie, Marinesco), and, microscopically, the connective-tissue web is thickened and proliferating. The ganglion-cells are often reported as exhibiting evidences of degeneration." . . . "Arnold has found vacuolization; not infrequently considerable deposits of pigment are seen within the cytoplasm. But, as in Case II, the ganglion-cells may be normal; the Nissl bodies are present in normal arrangement, volume, and shape, and show no deviations in their staining reactions; and the pigmentary deposit is not abnormally abundant. The sympathetic ganglia in the case reported by Gauthier were also normal. It is advisable, at this point, to call attention to the fact that the interstitial hyperplasia is by no means a lesion characteristic of the sympathetic system, but is simply an extension of the general process so often alluded to. The growth of connective tissue in the sympathetic may depend in part on lesions in the walls of the vessels; or both may be referable to the common factor of deranged nutrition.

"*Cord and Medulla.*—The pathological findings in both the cord and medulla differ greatly. Virchow, and also Fritsche and Klebs, have reported hypertrophy of the medulla. The spinal cord was enlarged in the case reported by Linsmayer. Many observers have reported various degenerations in the cord. Baruch's case was associated with symptoms of syringomyelia; Debierre gives a case with diseased posterior columns, while Arnold, Dallemagne, and Tamburini have found at autopsy irregular degenerated areas in the cord, affecting, however, no special place with any degree of constancy."

That the trophic changes in the nerve-tissues explain several of the neurological and myological symptoms in acromegaly is obvious, but these occur in *advanced* cases, *i.e.*, when such morbid changes have had time to occur. The signs which point to the posterior lobe as the seat of an important center—in keeping with physiological data enumerated on page 510—occur during the *early* or erethic stage, viz., the painful hyperæsthesias in the extremities, the tingling, numbness, the vasomotor neuroses and the palpitation. Their presence is explained by the marked rise of blood-pressure produced by irritation of the pituitary body proper, observed by Cyon, and confirmed by Masay, and by the long-recognized identity of the posterior pituitary as the *neural lobe, its histology and nervous connections.*

Pending additional evidence in this direction the nature of the process through which the pituitary influences the nervous system requires study.

THE HISTOLOGY AND PHYSIOLOGICAL CHEMISTRY OF THE NEURON.

We are first brought to inquire into the relationship between the modern conception of the structural composition of the cerebro-spinal axis and the views I have submitted. Granted, therefore, that the posterior pituitary body is the seat of a process through which chemical energy is converted into nervous energy, and that this constitutes the nervous impulses which the cerebro-spinal axis transmits to the various organs, how do the nerve-elements utilize this energy when functionally active?

I refer, of course, to Waldeyer's neuron as the morphological unit of the cerebro-spinal axis, and the processes of which are not in contact, but sufficiently close, one to the other, as to make it possible, when required, for a nerve-impulse to cross the interval between them. These facts have been satisfactorily established by modern methods, especially through the labors of Golgi and Ramón y Cajal. But the manner in which the gap between the processes is closed—*i.e.*, how the impulse passes from the terminal brush of the axon of one nervous element to the dendrites of the next—is still to be determined. It has been suggested, however, that the processes behave, in a limited manner, as do the pseudopodia of the amœba, and that by a slight extension the interval between the processes is closed. When the processes are not in contact they are said to be in a state of "retraction." Much as such a function would facilitate and shorten our analytical work could incontrovertible experimental facts be adduced to sustain it, we are brought, by a review of the literature of the subject, to recognize that such facts are not available. Indeed, the majority of physiologists and neuro-histologists now consider the question of "amœboid movements of the neuron" in the light of a working hypothesis.

There is one feature of the investigations in this direction which may serve to throw more light upon the whole question if one of the more prominent deductions submitted by me in the present work is taken into consideration: *i.e.*, the fact that certain drugs cause overactivity or insufficiency of the adrenals.

Much of the physiological work done in connection with the neuron includes the administration of various toxics,—strychnine, chloroform, morphine, etc.,—and amœboid movements or other active manifestations of the protoplasmic processes are thus ascribed to the action of the drugs upon the neurons *per se*, whereas, in the light of my views, the changes of form witnessed should be ascribed to increased or reduced blood-supply when toxic doses are given. To illustrate my meaning I will give in outline an experiment which represents one of the key-stones of the entire theory, that of Demoor. Before doing this, however, it may, perhaps, be well to state that I will consider the terms *"neuron"* as applying to the complete nerve-cell, including processes; *"neuraxon"* to the (usually) single and long process which extends along the center of the nerve-fiber, and is then called "axis-cylinder; "*dendrites*" to the cell's many processes—some of which end in many branches or tufts—other than the neuraxon. With Foster and Sherrington we will consider that neuraxons carry impulses *away* from the cell, while dendrites transmit impulses *into* the cell. Two other prominent morphological features are the "*gemmules*"—minute projections all along the dendrites—and their terminal twigs, which recall those on the stems of the moss-rose, and the *varicose*, or irregular, swellings that may be observed in the course of the dendrites or their terminal twigs.

The experiment of Demoor was briefly as follows: He *killed* a dog by injections of morphine; a second dog was given morphine for some time, then killed by cutting the medulla; a third was trephined. The next day a piece of the left hemisphere of the latter dog was removed; the animal being then morphinized, another piece—but of the right hemisphere this time—was removed. Portions of the hemispheres of the two killed dogs having also been removed, all specimens were treated in precisely the same manner. The cellular changes were found to be similar in all specimens taken from the morphinized animals: their gemmules had disappeared. Alone of the series the piece removed before morphine had been given was covered with regularly distributed gemmules. Now the fact I wish to emphasize is this: while this experiment is thought by its author to show that the retraction of the gemmules constitutes the inactive state, as induced by morphine through the *local* action this drug is now thought to have upon nerve-cells, the retraction of the gemmules is due to general vasoconstriction of all arterioles, *including those of the adrenals*, by a direct action of the morphine upon the sympathetic center. (See page 1272.) We thus have, instead of a purely local effect, an example of the general physiological process through which the neuron passes from the active to the passive state, the circulation of oxidizing substance in the neuron being thus inhibited.

Again, the same structures treated by different methods have been found to yield different results. Thus, H. H. Bawden[22] found that "all material treated according to the slow method of Golgi shows, as a rule, an almost absolute freedom from varicosities; varicose cells occasionally occur." The mixed method and the rapid were found to yield practically the same results when the dendrites had taken the stain: the gemmules were almost invariably present and regular. In some sections almost every dendrite was varicose; in others hardly any. All these results were similar whether normal or "toxic" material was used, and the author concludes that "it is impossible for an unprejudiced observer to differentiate or distinguish between the two kinds of material." Lugaro,[23] who has upheld the retraction theory, also reached the conclusion that "imperfect fixation is very largely, though not entirely, responsible for the formation of varicosities and the disappearance of gemmules." Weil and Frank summarize what a review of the literature of the subject shows, when they say: "The findings have been in almost every case positive, although there are occasionally records of negative results and even contradictions,—as, for example, between the investigations of Demoor and of Soukhanoff on the effects of chloroform. . . . Retraction of the gemmulæ and coincident swelling of the dendrites form the essential features of every description."

Judging from the foregoing estimates as to the effects of stains upon dendrites, these phenomena are to be considered as artifacts: *i.e.*, as artificially produced changes. Under these conditions, it is clear that the latter should appear, irrespective of the condition of the animal at the time of its death: *i.e.*, whether under the influence of toxics as stated, fatigue, etc.

That prevailing views in this connection are erroneous is my firm belief after a critical analysis of available experimental evidence. Particularly instructive and valuable in this connection are the experiments of H. H. Goddard,[24] which consisted "in cutting through the entire head of the animal at a single blow with a very thin sharp knife, the parts of the head falling instantly into large dishes of Cox's solution warmed to 39° C. In his first experiment, puppies about seven weeks old, sisters from the same litter, were used, the one while somewhat tired, the other after having slept. A careful count of the pyramidal cells of the cortex of the somewhat fatigued puppy gave a proportion of 31.1 per cent. of cells showing varicosity, while cells from the same region of the puppy killed after sleeping was 8.5 per cent. In the former animal 15.9 per cent. of the cells showed much varicosity; in the latter only 0.8 per cent. showed a similar state. In the second experiment the first of two sisters was killed on waking in the morning; the second at night when tired and very sleepy. While it "was difficult to find a single varicosity on the dendrites of the morning puppy, for long distances in the cortex of the evening puppy" it was difficult to find a cell "whose processes" were "not more or less varicose." It is evident that in these instances at least the stain was not alone the source of varicosities, since it was only in the tired puppies that the varicosities were very marked, while in the thoroughly rested animal practically none could be found.

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[22] H. H. Bawden: Journal of Comparative Neurology, May, 1900.
[23] Lugaro: Rivista di patol. nerv. e ment, vol. iii, 1898.
[24] H. H. Goddard: Jour. of Compar. Neurol., Nov., 1898.

Judging from these experiments, varicosity of the dendrites coincides with a fatigued condition. This corresponds exactly with the experiment of Demoor, previously described, since retraction of the gemmules is accompanied by varicosity; so that fatigue and a large dose of morphine must have produced similar results.

If the staining process alone caused the formation of varicosities in Demoor's experiments,—the same method having been used for all specimens,—how is it that one of the latter showed gemmules (which means absence of varicosities), and that this solitary specimen is precisely from the only animal which had not received morphine? Berkley[25] found that poisoning with alcohol "in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum" very similar in character to the pathological lesions produced by other more virulent soluble poisons. The terminal twigs of the dendrites were also found to have become varicose or beaded, the gemmules being very scarce or absent. Here, again, is a condition which, as does fatigue, morphine, and, we may add, chloroform, chloral hydrate, and other toxics used by Demoor and others with similar results, all tend in the one direction: *i.e.*, to morbidly reduce functional activity. This is a well-known characteristic of the bromides. In a study of the cortical cells under the influence of poisonous doses of potassium bromide, H. K. Wright[26] says: "If the primal ascending dendron is followed to its visible termination, several ampullous or varicose swellings of varying size are met with," . . . "on the basal processes also varicosities are to be seen; but they are small and, like those of the ascending protoplasmic process, are sharp in outline, and shorn of the lateral projections which obtain on the unaltered part of the extensions. One may be seen on each secondary branch, and ranges in size from a small and *scarcely recognizable* to a *readily obvious* swelling. None of them, however, reach the dimensions of the apical projection and its branches."

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[25] Berkley: Brain, Winter, 1895; and Johns Hopkins Hospital Reports, vol. vi, 1897.

If the method of staining is the cause of all this, we are brought to the conclusion that it must be selective as to the parts of the dendrite it affects, and that only functionally-impaired cells are so affected by the stain as to show varicosities. Even then staining methods would furnish precious indications. But it seems clear to me that, while the newer chrome-silver methods still furnish imperfect pictures of the morbid alterations of the neuron, they cannot with justice be said to either cause or prevent the formation or disappearance of gemmules and varicosities; in other words, that they are not artifacts of the Golgi method. The marked tendency of the swellings to locate at the apices, and the gradual reduction of the varices as the cell-body is approached recall, on the other hand, a well-known pathological principle: *i.e.*, that the morbid effects of impaired general nutrition are first felt by terminal structures.

And the painstaking experiments of Weil and Frank do not appear to me in the least to prove their conclusions that "the varicosities must be regarded as artifacts" and that "they depend for their presence and their amount on the form and method made use of." Demoor employed the same method in each of his *comparative* experiments and his results were not similar, the non-morphinized specimen alone differing from all others. Hubbard used the identical method in both his *comparative* experiments, and likewise obtained results which distinctly showed a marked difference between the rested and fatigued animals. In these and other experiments referred to, the pathogenic agency, including fatigue, was allowed sufficient time to produce alterations in the cortical cells, if *nutrition* has anything to do with the process.

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[26] H. K. Wright: Brain, Summer, 1898.

In Weil and Frank's experiments the animals were overwhelmed by the quantity of toxic administered, and death occurred, viewed from my standpoint, by arrest of the adreno-cardiac functions, long before any *marked* action upon the cells could possibly have occurred. The doses of morphine administered were 0.38 and 0.41 gramme (6 and 7 grains), respectively, with death in 15 minutes; of strychnine nitrate, 0.018 gramme ($^1/_3$ grain), death in 20 minutes; of hypertoxic urine, 125 to 150 cubic centimeters (4 to 5 ounces), death in 15 to 25 minutes. That these are overwhelming doses in rabbits is evident. One animal was killed with serum (30 cubic centimeters—1 ounce) in 5 minutes; others with clhoroform inhalations in 10 minutes; one by tracheal clamping in 8 minutes. The rest, six animals, were destroyed instantly by instrumental procedures. In none of these animals was there any distinction established as to whether they had been sleeping, eating, or romping, etc. That some were old and others young in the series of nineteen is probable; as is well known, erethism, especially in such delicate structures, is greatly influenced by age, and a few months in the rabbit represent as many decades in man. The weight of each animal was not recorded in order to establish the relative action of a given dose of the toxic used per pound of animal, though, of course, in the experiments, the large doses used precluded any usefulness on this score.

Finally, the authors themselves will surely admit that "no varicosities," "varicosities," "slightly varicose," and "very slightly varicose," the method of notation utilized by them, conveys but little exact information. And still, even this sustains a deduction opposite to theirs. Indeed, the short period of time that elapsed between the injection of the toxics in the animals killed in this manner—represented by 108 blocks of slides—must have sufficed to initiate retraction of the gemmules and the formation of varicosities, since only 10.2 per cent. of these blocks show no varicosities. When, on the other hand, the proportion of animals killed instantly by instrumental procedures—93 blocks of slides—is analyzed, over two and a half times as many, *i.e.*, 28 per cent., are found to show *no* varicosities.

But a fair question suggests itself in this connection: Why do the remaining 72 per cent. show any varicosities? Only 14 per cent. of the blocks from the instantly killed animals are recorded as "varicose," the remaining 58 per cent. being entered as "slightly" or "very slightly" varicose. In their explanation of the scope given these terms, the first means "at least some varicosities" and the second as "only very few varicosities." Now, the authors state that "in the first nine cases here recorded the brains were placed in fixing fluids within three to five minutes." Nothing is said of the rest; so that we may infer that the ten other brains were immersed after longer intervals. We have previously seen, when the conversion of myosinogen into myosin was studied, that oxidation processes continued even after death: *i.e.*, until all the oxygen had been utilized. That this must be the case with the brain, which contains one-fifth of the blood of the whole body, and that products of metabolism, especially CO_2, should form in the entire encephalon is evident. It normally follows that we have in this factor a potent cause for the retraction of gemmules and the formation of varicosities.

Indeed, the contrast between the results reached speaks for itself when compared to those of Goddard, who resorted to procedures in which the exact condition at the instant of death were preserved, "the parts of the head falling *instantly* into large culture dishes warmed to 39° C." Even continuation of the normal brain temperature was insured. And what were Goddard's results? "It was difficult to find a single varicosity on the dendrites of the morning puppy,"—*i.e.*, the thoroughly *rested* animal; while in the thoroughly *tired* one "for long distances in the cortex . . . it is difficult to find a cell whose processes are not more or less varicose." That fatigue is the result of an accumulation of products of metabolism and especially CO_2 is generally recognized.

Goddard's procedure appears to me to represent as nearly perfect a one as available staining methods (Cox's and the rapid method show considerable parallelism in Weil and Frank's report, while the mixed and slow methods appear unreliable and contradictory) will allow; *his results, in my opinion, portray the actual changes that are produced in the neuron under the influence of certain poisons and during sleep:* i.e., *when the blood-supply of the brain is reduced.*[27] (See plate p. 1264).

Weil and Frank state that they "are able fully to corroborate the statement of Cajal that normal and toxic material cannot be differentiated by the number of varicosities or of gemmules." The care with which such experiments must be conducted, apart from the method of staining adopted; the need of immediate immersion, and other details to which we have referred, invalidate any opinion that the distinguished Spanish histologist may have expressed on this score, unless he can show that his experimental *physiological* procedures were as perfect as his staining work must have been. Indeed, I must express the belief that the greater part of the physiohistological work done so far in this connection is valueless owing to the absence of the precautions to which I refer.

Again, Ramón y Cajal's conclusions that "the nerve-cells do not move, but on the other hand, that the neuroglia-cells do move" (which underlies his view as to the gemmules and varicosities showing no difference when normal or "toxic"), has been shown by Dercum to embody its own refutation. "Cajal," says the latter author, "points out the fact that the processes of the neuroglia-cells have numerous short arborescent and plumed collaterals, and he states that in these cells two different phases can be observed: first, a stage of contraction,—that is, a stage in which the cell-processes become shortened; and, secondly, a stage in which the cell is relaxed,—that is, a stage in which the processes of the neuroglia-cells are elongated. He maintains that the processes of the neuroglia-cells represent an insulating and non-conducting material, and that during the stage of relaxation these processes penetrate between the arborizations of the nerve-cells and their protoplasmic processes, and so make difficult or impossible the passage of the nerve-currents; on the other hand, in the stage of contraction the processes of the neuroglia-cells are retracted, and they no longer separate the processes of the nerve-cells, and the latter are thus *permitted to come into contact.*[28] Evidently Ramón y Cajal admits the very thing against which he contends, for if the nerve-cell processes are at one time not in contact and at another are in contact, they must certainly move, and the question before us is self-admitted. It matters not whether the processes of the nerve-cells move little or much, but that they move at all is the question at issue, and this Ramón y Cajal admits, though he makes the movement a purely passive one."[29] To me it appears clear that, since Ramón y Cajal held the nerve-cell to be a passive structure, requiring an independent connecting-link to close the circuit with the adjoinng cell, he must have denied both the gemmules and the varicosities any physiological importance. His opinion, therefore, that normal material cannot be differentiated from toxic material, when applied to the retraction of gemmules and the formation of varicosities, cannot be said to rest upon solid premises, and, for the time being at least, to in no wise affect the question.

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[27] We wish to particularly emphasize the fact that we are in no way criticising adversely the work of Drs. Weil and Frank. We have nothing but praise to express for these investigators. Much of the searching inquiry to which we are submitting their paper includes the use of features introduced for the first time in the present work, and obviously unknown to them. Indeed, if our views eventually prove to be sound, we will owe much to the counter-evidence Drs. Weil and Frank—and, we may add, Dr. H. Heath Bawden—have published.—S.

In a comprehensive review of the anatomy and physiology of the nervous system, L. F. Barker[30] makes the following remarks: "The physiologist of the present day sees in the functions of the nervous system, even in those which are most complicated, only certain manifestations of energy. Moreover, he believes that in neurons, as in all other cells of the body and as in the world generally, the law of the conservation of energy during transformation holds, and consequently regards the phenomena of irritability, as exhibited by a neuron or by groups of neurons, as the kinetic representative of the potential forces of the cells and their foodstuffs. The metabolic activities and the vital manifestations of the cell are concomitant processes—another example of the inseparable connection which exists between what we term matter and energy. There has been in many quarters a certain amount of hesitancy in accepting the view that the capacities of the nervous system, particularly those of the brain, are dependent directly upon the chemical and physical alterations which are continually going on within its constituents: a hesitancy which, though it has in the past proved a serious obstacle to progress, is happily now fast disappearing. For the plant, all the evidence goes to prove that under the influence of sunlight and heat marked chemical and physical changes take place within it which we recognize in its vital processes. In the animal—be it granivorous, carnivorous, or, like man, omnivorous—it is the chemical energy introduced as food which represents, in the main, the source of the energy of the organism. . . . *The physiologists have been struggling for fifty years or more to gain an insight into the nature of what they call nerve-impulses,* by which is to be understood the occurrences inside axons: for example, at the time when we have good reason to believe that they are functionally extraordinarily active. Their efforts have supplied us with a multitude of data, physical and chemical, interesting enough, no doubt, but which can serve as only the barest prolegomena to an explanation of the essence of the occurrences. If we are so badly informed concerning these elementary and fundamental phenomena we may very well be content to be modest for some time to come in our claims as regards a physiological psychology. It is by no means impossible that in the nervous system forms of energy are concerned which do not exist outside the animal body and which yet remain to be recognized and studied. . . .

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[28] We will see farther on that Cajal's observation as to the relaxation and contraction of neuroglia-cell processes is valuable in that it proves that the tips of the gemmules do not transmit nervous energy.—S.

[29] Dercum: University Medical Magazine, April, 1897.

[30] L. F. Barker: New York Medical Journal, May 15 *et seq.*, 1897-98.

Truly, to find out the properties of a single neuron would be a task appalling enough; but, when we remember that of the millions of neurons in one individual perhaps no two are just alike, the quest would seem hopeless. But instead of burying ourselves in pessimistic reflections, or being discouraged by what is at present unattainable, by what may perhaps forever remain to us unknowable, we may profitably turn to the consideration of some of the points which lie more within our ken. One point, self-evident enough when one's attention is directed to it, but which often appears to have been overlooked in connection with the neurons, is the unremitting character of their activity. With a metabolism as complicated as that occurring within the nerve-units it is inconceivable that there can be any period in which alterations in chemical structure, and consequently energy transformation, are not going on. From moment to moment, throughout all the hours of the day and night, analytical and synthetic processes are taking place, associated with the alterations in physical forces which necessarily accompany these changes. In common with everything that lives, the neurons know no absolute repose. As I have said, in speaking of their metabolism, periods of extravagant activity may alternate with periods of more economic change, but total rest is inconsonant with continuance of existence. We are forced to believe that what we ordinarily speak of as the passage of a nerve-impulse represents, as it were, *a stormy process in the nerve-fiber,* and that just as absence of a storm does not mean absence of weather, there are in all probability minor alterations—currents, if you will—passing to or fro or *passing to and fro in a given nerve-fiber in the intervals* between the more violent excitations."

The words that I have italicized will doubtless recall some of the more prominent features previously emphasized in respect to the relative nervous processes involved in the functions of the various organs reviewed. I have termed "passive" that form of energy continuously transmitted to tissues and vessel-walls. A quiet and steady flow of blood into the cellular structures, sustained by the tonic contraction of the arteries, and a stream of nervous impulses to the tissues coinciding in rhythm, perhaps, with that sent to the vessels, suffice to insure nutrition and to hold the structures thus supplied ready for active work. What is the source of *this* energy?

If the posterior pituitary reinforces the flux of impulses when functional activity is demanded, passive energy would seem to require another source, and as the lower, or middle, brain and the cord are included in the "sphere of influence" of this organ, the hemispheres are the only parts of the encephalon that can supply the need. But they do not. Removal of the hemispheres, we have seen, does not impair muscular activity; a frog can jump, a pigeon can fly, etc., and, after a short period of shock-paralysis immediately after the operations, movements return—evidence that their nutritional metabolism, incited and regulated by nervous impulses, continues. Evidently, therefore, the hemispheres have nothing to do with the process; they are solely the seat of the "mind," and constitute an organ among the rest, itself supplied with vasomotor nerves (Obersteiner, Gulland, Huber, Hürthle, Cavazzani, François-Franck, *et al.*), and probably with its own nutritional nerve-system. We are, therefore, brought back to the posterior pituitary as the only organ capable of satisfying the needs of the situation: *i.e.*, as the only source of passive energy.

This suggests that metabolism may suffice, through the agency of the blood's oxidizing substance, to sustain physiological activity during the intervals between "stormy processes of the nerve-fiber"; but this is promptly shown to be a wrong interpretation when the effects of section below the medulla are recalled. As all the arteries of the organism are immediately relaxed, a continuous stream of impulses must have served to hold the vessels in tonic contraction: evidence that passive nervous energy is a factor to be reckoned with. Thus, the fact that all co-ordinated muscular movements continue after removal of the hemispheres relegates to the lower brain the function of supplying active energy—and, obviously, passive energy likewise, the need of the latter being shown by division of the medulla. Indeed, *passive* energy may well be described as passing to and fro in a given nerve-fiber in the intervals between the more violent excitations, while *active* energy can as fittingly be likened to "a stormy process in the nerve-fiber": both ascribable, it now seems likely, to the one organ, the posterior pituitary body.

To establish the functions of the posterior pituitary within its proper physiological limits, however, it is necessary to ascertain how nervous elements in general and neurons in particular are nourished, since it is upon the degree of perfection with which the nutritive processes are carried on by the blood that the functional integrity of these structures depends.

The fact that a *general* nutritional process prevails, of which the adrenal system is the primary motive agency, I have shown; but it finds further support in the following statements of Professor Barker's—which, of course, but emphasize a generally known fact—that, "in the absence of substances in the body derived from the thyroid gland, the nervous system undergoes very important and serious metabolic modifications, evidenced by the remarkable nervous and mental phenomena with which all are now familiar. On restoring these substances to the body by the administration of a thyroid extract the symptoms may sometimes be made to disappear. It is likely, however, that the neurons find their staple foods in the main nutritive constituents of the blood as derived from the food digested in the stomach and intestines and purified by the lymph-glands and liver."

I have, I believe, satisfactorily shown that the thyroid secretion incidentally sustains the activity of the anterior pituitary body, and therefore of the entire adrenal system, by pouring its secretion into the blood. The functions of the digestive organs we have also reviewed. Among the latter, however, are two upon which I laid considerable stress,—*i.e.*, the spleen and pancreas,—and I called attention to the great importance of trypsin—the splenopancreatic ferment—in the conversion of albuminoid substances, and especially of their toxic derivatives, into benign products. These albuminoid substances, we have seen, then pass through the liver, and, after traversing the cardiopulmonary circuit are distributed broadcast throughout the organism. There is a feature which I kept in abeyance, however,—though a well-known one,—since at the time its true weight would not have asserted itself: *i.e.*, the fact that *albuminoids include nucleins derived from the animal and vegetable* *cells ingested with food, which nucleins contain at least 3 per cent. of phosphorus.* We can now realize how great is the physiological rôle of the pancreas and of the spleen in the organism.

Indeed, the functions of these two organs may be said to constitute one of the pillars upon which the vital functions rest. As a constituent of calcium phosphate, phosphorus is found in the bones, teeth, cartilage, and other tissues; in the blood, milk, etc., in quantities which bespeak of its functional prominence, since calcium phosphate is represented by nearly six *pounds* among the organism's constituents. Sodium phosphate—which gives the blood, lymph, and other body-fluids their alkalinity and fluidity, and the potassium and magnesium phosphates, which fulfill much the same rôle, obviously find in phosphorus their main dynamic attributes. But it is when we reach the nervous system that the functional worth of this element reaches its highest mark.

How are nervous structures—neurons, axis-cylinders, sheaths, etc.—adequately supplied with blood-plasma, their oxidizing substance, their phosphorus, etc.?

THE PHYSIOLOGICAL CHEMISTRY OF NERVES.—The functions of myelin, or white substance of Schwann—a jelly-like homogeneous and transparent material which surrounds the axis-cylinder of nerves, and is only separated from it by a thin protoplasmic film—may be said to be unknown. It is a fatty substance, blackened by osmic acid, and which, after death, coagulates and becomes opaque, loses its homogeneity, etc. Myelin is now universally considered as a protective coat: a function which the overlying neurilemma already fulfills. Is myelin fatty in the true sense of the word? Examined chemically in quantities, a very large proportion of dried nerve-substance—about one-half, according to some observers—consists of a peculiar body: *cholesterin.* This body is not a fat, but an alcohol; like glycerin, however, which is also an alcohol, it forms compounds with fatty acids. "Though we do not know definitely the chemical condition in which cholesterin exists during life in the medulla," says Professor Foster, "it is more than probable that it exists in some combination with some of the really fatty bodies also present in the medulla, and not in a free isolated state." . . . "Besides cholesterin, 'white' nervous matter contains a less, but still considerable, quantity of complex fat whose nature is disputed. According to some authorities rather less than half this complex fat consists of a peculiar body, *lecithin*, which we have already seen to be present also in blood-corpuscles and in muscle. Lecithin contains the radical of stearic acid (or of oleic, or of palmitic acid), associated, not—as in ordinary fats—with simple glycerin, but with the more complex glycerin-phosphoric acid, and further combined with a nitrogenous body, *neurin*, an ammonia compound of some considerable complexity; it is therefore of remarkable nature, since, though a fat, it contains both nitrogen and phosphorus." Cholesterin ($C_{26}H_{44}O$), lecithin ($C_{44}H_{90}NPO_9$), and neurin ($C_5H_{15}NO_2$), as shown by the formulæ, are all oxygen-containing bodies. May this supposed coating and insolating material, myelin, not be to the nerve what myosinogen is to muscle?

Cholesterin, we have seen, is associated with hepatic functions. "It is singular," says Professor Foster, "that, besides being present in such large quantities in nervous tissue, and to a small extent in other tissues and in blood, cholesterin is a normal constituent of bile." I have previously referred to the fact that this alcohol, the only one which occurs in the body in a free state, combines with glycocholic acid in the formation of bile, and is thus eliminated by the liver. This view sustains that of Austin Flint, who looked upon cholesterin as an excrementitious product derived from the nervous system: *i.e.*, the result of nerve-metabolism. Cholesterin is present in abundance in the white substance of the cerebro-spinal axis, as well as in the myelin, or white substance of Schwann, in nerves. We have seen, however, that the elimination of excrementitious products by the liver is carried out by the combination of various agencies: mainly glycocholic and taurocholic acids derived from cholic acid through an oxidation process in which the oxidizing substance plays the predominating rôle. That an oxidation process also occurs in a nerve during functional activity is suggested by the following lines of Mathias Duval: "Direct experimentation has shown that the functionating nerve is the seat of *increased combustion;* this is accompanied by the liberation of heat, the presence of which Schiff has demonstrated even up to the nerve-centers, under the influence of fear, of excitation of the senses, of any cause —in a word—which produces cerebral activity."

Lecithin—"a conspicuous component of the brain, nerves, yelk of egg, semen, pus, white blood-corpuscles, and the electrical organs of the ray"—suggests its identity as at least one of the sources of energy we are seeking by the fact that if merely allowed to stand at the ordinary temperature its solutions acquire an acid reaction and are decomposed. In the intestines it sometimes breaks up into its constituents: fatty acids, glycerin, phosphoric acid, and *cholin* (Howell). Neurin is, in reality, cholin, and therefore a decomposition product of lecithin. As previously stated, Tappeiner[31] obtained fatty acids as a result of cholic-acid oxidation. These facts, of course, are only cited as mere landmarks to indicate that we are dealing with oxidizable bodies. As far as the nerves themselves are concerned, therefore, it seems probable that we have in lecithin an agency capable, by the character of its molecule,—*i.e.*, carbohydrates, phosphorus, etc.,—of acting as a potent source of working energy when brought into contact with the oxidizing substance; and in cholesterin the main waste-product of nerve-catabolism.

Admitting, then, that we have in the lecithin of myelin a body capable of acting as a source of energy in a way similar to myosinogen in muscle, how does the oxidizing substance of the blood-plasma reach it? The nodes of Ranvier and the neurilemma that covers them allow silver stains to reach the axis-cylinder, but the myelin itself does not permit of this. This suggests that the nodes themselves—*i.e.*, the rings forming them—may allow the blood-plasma to filter through them, thus bringing the oxidizing substance in immediate contact with the axis-cylinder. The finer anatomy of nerves indicates that such may be the case. Indeed, the nodes referred to occur at regular intervals, and separate the nerve, as is well known, into as many segments, which recall, in a measure, the muscle-fiber and the liver-cell or, at least, features characteristic of both these structures. If the blood-plasma can penetrate the nodes of Ranvier as do stains, there only lies between it and the axis-cylinder an extremely delicate layer of protoplasm,—Mauthner's sheath,—which in no way would impede the entrance of the fluid into the axis-cylinder itself.

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[31] Tappeiner: Zeitschrift für Biologie, Bd. xii, S. 60, 1876.

The term "cylinder" suggests the tubular shape of the latter: in accordance with Remak's view that it consists of a delicate, longitudinally striated tube, filled with an albuminous liquid. The prevailing view, however, is that of M. Schultz, who considers the axis-cylinder as made up of fibrils united by an intervening unknown substance. This seems to me to vividly recall the arrangement of muscular fibers as regards their relation with the blood-plasma: *i.e.*, minute fibers into which the plasma may freely enter. Again, we must not lose sight of the fact, in this connection, that the axis-cylinder is nothing but the elongated axon of a neuron, and that the fibrillæ now referred to, therefore, represent the intimate structure of a neuron's axon. Now, as Schäfer holds that these fibrillæ are extremely fine tubes filled with fluid, and as the character of this fluid is not known, I have good reason to believe that *they are channels for the blood-plasma:* i.e., *for the oxidizing substance.*

But there is another feature which points to the axis-cylinder as a channel for the oxidizing substance: *i.e.*, the fact that the so-called "medullary sheath"—*i.e.*, the myelin itself—contains a supposed "supporting frame-work." The striæ representing them were at first termed "clefts" or "incisures" by Schmidt, Lautermann, and others, but Ranvier considered them as protoplasmic septa which subdivide each internodular segment of the nerve into several conico-cylindrical chambers. W. H. Wynn,[32] who gives an excellent review of this subject and the results of personal researches, refers to those of Rezzonico[33] and Golgi,[34] who "from the examination of fibers treated by a mixture of bichromate of potash and osmic acid, and afterward by nitrate of silver, find that each cleft is occupied by what appears to be a thread of darkly-stained substance passing *spirally around the fiber*. They consider," he

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[32] W. H. Wynn: Journal of Anat. and Physiol., April, 1900.

[33] Rezzonico: Archivio per le Sci. med., Torino, vol. iv, 1880; and Gazzetta med. ital. lomb., Milano, vol. i, 1879.

[34] Golgi: Arch. per le Sci. med., Torino, vol. iv, 1880.

adds, "that the supporting frame-work of the sheath consists of *a chain of funnels* surrounding the axis-cylinder, each funnel being formed by a spiral thread." Tizzoni[85] "believes that there is but one net-work closely investing the axis-cylinder, and that it is *in connection with* the slits of Lautermann." McCarthy is stated to have shown that, "after a nerve has been hardened with picric acid and ammonium chromate, the medullary sheath contains minute, rod-like structures, which pass rapidly between the axis-cylinder and the primitive sheath so as to give the cross-section of a fiber the appearance of a wheel. The rods stain with carmine and hæmatoxylin, which do not stain the myelin. It is not possible to isolate the rods as separate elements, for they are not distinct from one another, but united." Finally he refers to the fact that Lautermann, von Stilling, Roudanowski, and McCarthy all believe that there is "a system of *hollow canals* in the sheath of the axis-cylinder," and himself reaches the conclusion that the cones they form are protoplasmic, and not composed of neuro-keratin, as is usually held. He divides "each cone into six segments placed at regular distances apart and converging from the primitive sheath to the axis-cylinder." This is well shown in the annexed illustration, reproduced from his paper. If we now consider the segments as canaliculi leading from the axis-cylinder, we can readily see how the blood-plasma can penetrate the myelin and its oxidizing substance, and these bodies carry on, when brought into contact, a reaction similar to that which occurs in muscle-fiber. Indeed, if the various features enumerated are collectively considered, it will become apparent that *the myelin, or white substance of Schwann, when in contact with the oxidizing substance of the blood-plasma undergoes a reaction in which chemical energy is liberated.*

When we consider that the axis-cylinder is, as stated, the continuation of a neuron's axon, it is not difficult to account for the various phenomena, known under the general term of "nerve-degeneration,"—*i.e.*, the disorganization of myelin, the dissolution of the myelin, etc.,—at the distal end of a nerve, when the latter has been cut. Very suggestive, in this connection, are the following lines by Professor Barker[36]: "Waller proved that if a motor nerve was severed there resulted complete degeneration of the fibers in the peripheral end, even to the muscles which they govern, the central end remaining apparently intact. As a matter of fact, the changes characteristic of the Wallerian degeneration could not, as a rule, be traced farther in the central end than to the first node of Ranvier." Stewart[37] states that "in the degenerated nerve

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[85] Tizzoni: Archivio per le Sci. med., vol. iii, fasc. 1, 1878.

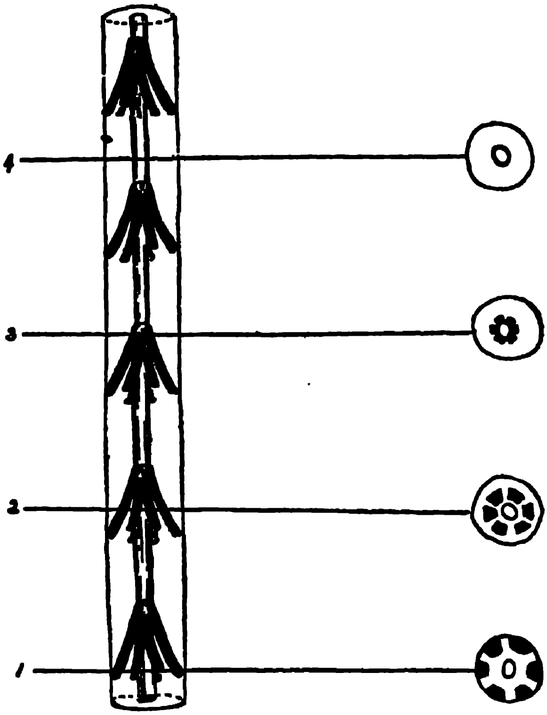

Diagram of Relation Between Longitudinal and Transverse Sections, Showing Cones Cut Across at Different Levels.

1, at base of cone; 2, through middle of cone; 3, through apex of cone; 4, through interval between two cones. In 1, 2, and 3 the cone segments and protoplasmic sheaths are seen. In 4 only the thin protoplasmic sheaths beneath primitive sheath and around axis-cylinder are visible. (*W. H. Wynn.*)

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[36] Barker: *Loc. cit.*, p. 740.

[37] Stewart: "Manual of Physiology," p. 607.

the substances soluble in ether are relatively increased owing, in part, to fatty degeneration of the axis-cylinder," and that "the percentage of phosphorus is markedly diminished (Mott and Barratt)."

Another process which seems to acquire a certain degree of light is nerve-regeneration. It is obvious that if we grant the axis-cylinder, as the extension of the axon, all functional and nutritive attributes, we may easily explain peripheral nerve-degeneration, but not regeneration, the peripheral segment being unprovided for by reason of the section. We know, on the contrary, that a piece of the nerve must be removed in order to prevent reunion, and that otherwise in two or three weeks, and often earlier, its functions will be restored. New cylinders and fibrils grow, acquire myelin, and, perhaps, guided and assisted by (nucleated) neurilemma, soon meet those of the peripheral segment and become connected with them. Physiological functions of a normal kind must underlie this process even in the peripheral end of the nerve; otherwise union would not take place. Finally (we can only refer to a few of the more prominent processes involved in the vast subject now claiming our attention) the functional phenomena that follow after division of the cord distinctly indicate the continuation of nutrition and the functional activity—though impaired—in the distal fragment. Foster, for instance, says: "In the mammal (dog) after division of the spinal cord in the dorsal region regular and apparently spontaneous movements may be observed in the parts governed by the lumbar cord. When the animal has thoroughly recovered from the operation the hind-limbs rarely remain quiet for a long period of time; they move restlessly in various ways; and, when the animal is suspended by the upper part of the body, the pendent hind-limbs are continually being drawn up and let down again with a monotonous rhythmic regularity suggestive of automatic rhythmic discharges from the central mechanisms of the cord. In the newly-born mammal, too, after removal of the brain movements apparently spontaneous in nature are frequently observed. But all these movements, even when most highly developed, are very different from the movements, irregular and variable in their occurrence, though orderly and purposeful in their character, which we recognize as distinctly voluntary." Indeed, the nervous energy that myelin and the oxidizing substance procure is that which allows a frog deprived of its hemispheres and its middle brain "to sink in water as though the animal were of lead."

The axis-cylinder composed of fibrils into which blood-plasma penetrates being continuous with the axon of a neuron, we are brought to realize the nature of the parallelism between the functional phenomena of the latter and those of the suprarenal glands to which I have already referred. But we must not lose sight of the fact that each "medullated" nerve-fiber is divided by the nodes of Ranvier into as many subdivisions, and that each internodal segment receives its own supply of plasma. Does the neuron receive its supply through this chain of segments, or, rather, through the axis-cylinder that passes through them? That the former mechanism alone prevails is improbable, since so prominent a part of the entire structure as its cell-body, the seat of its nucleus, would hardly be supplied in so indirect a manner. The very importance of its functions betokens the existence of direct supply. Does such a vascular system exist? Fortunately, we have not far to seek.

THE CIRCULATION OF THE NEURON.—Barker, in a review of the facts that have been adduced for or against the neuron doctrine,[38] concludes that "it may be said, with fairness, that the control instituted by hundreds of histologists in various parts of the world has practically in every instance in which the method of Golgi or the method of Ehrlich has been employed gone to confirm the conception that the neuron is a unit in the sense of Waldeyer." The latter investigator's words, giving the gist of his doctrine, are also quoted: "If we review the main advance, made certain by the anatomical investigations discussed, it lies, in my opinion, in the sharper limitation, now possible, of the anatomical as well as the functional elements of the nervous system (for such we have to consider the nerve-units-neurons), and also the discovery of collaterals, with their end-arborizations, by Golgi and S. Ramón y Cajal." The following lines of Waldeyer's are also quoted: "If we assume, with Golgi and B. Haller, the existence of *nerve net-works,* the conception is somewhat modified, but we can still retain the nerve-units . . ."—all of which tends to show that, while the neuron doctrine stands on a solid foundation, there is a stumbling-block in its way which has not as yet been removed. Especially is this true since the investigations of Apáthy, of Naples, who, after several years' study, has unquestionably demonstrated the existence of a net-work of what he terms "neuro-fibrils."

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[38] Barker: American Journal of Insanity, July, 1898.

That Apáthy's "neuro-fibrils" as well as Golgi and Haller's nerve net-works are *not* nerve-elements, but fine capillaries which serve for the circulation of blood-plasma, seems to me probable. In the following extracts the italicized words will serve to call attention to the various links between these structures and others that we have analyzed. Professor Barker summarizes Apáthy's views as follows: "Apáthy has been convinced for some twelve years that the nervous system is composed of two varieties of cellular elements entirely different from each other: nerve-cells and ganglion-cells. The *nerve-cells,* the architecture of which is quite in accord with that of *muscle-cells,* give rise, he thinks, to neuro-fibrils. A neuro-fibril, in turn, passes out *of a process of a nerve-cell* and then goes *through a number of ganglion-cells,* and ultimately, after leaving the last ganglion-cell with which it is connected, passes more or less directly to a muscular fiber or to a sensory cell. The neuro-fibrils are, as *conducting substance* for the nerve-cells, what the *muscle-fibrillæ are as contractile substance for the muscle.* The pathways to be followed by the neuro-fibrils are predestined from the earliest embryonic stages, for they correspond, according to Apáthy, to the *intercellular protoplasmic bridges.*" That we have all required elements in support of my belief is evident; we have seen that muscle-fibers are, in reality, delicate tubes; that vascular channels for the transmission of blood-plasma should be protoplasmic is as obvious as is the need of their penetrating into and out of the cells.

What appears to me as conclusive evidence is indirectly afforded by the deductions of Ehrlich, suggested by his study of the methods of staining living nerve-cells and their processes with methylene-blue. "Ehrlich found," says Barker, "that by injection of a solution of methylene-blue dissolved in salt solution *intra vitam* into the *blood-vessels* of an animal, the *axis-cylinders* of many of the nerve-fibers (see Fig. 1), as well as numerous (particularly sensory) nerve-endings (see Fig. 2),

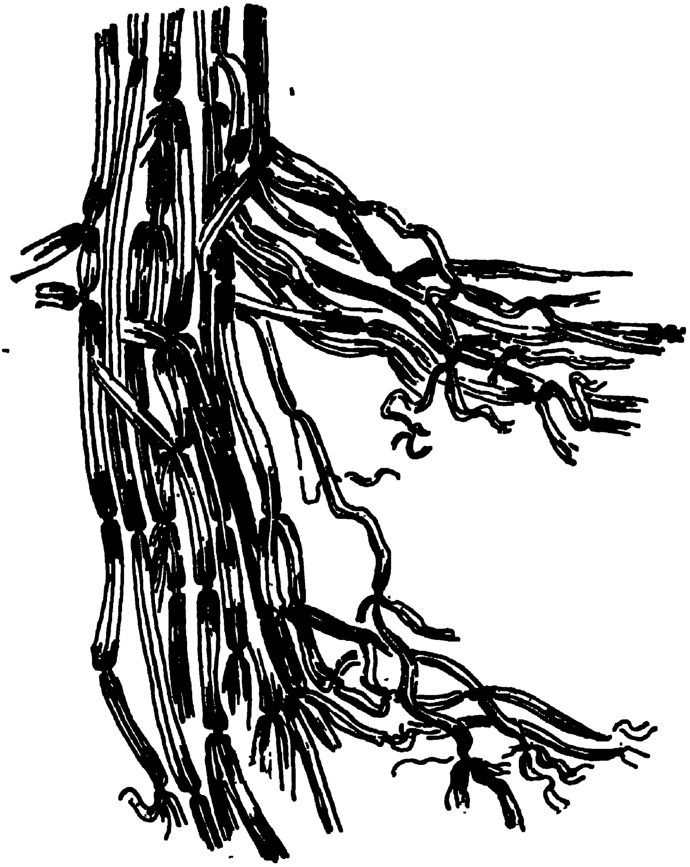

FIG. 1.—NERVE-FIBERS FROM A FROG INJECTED WITH METHYLENE-BLUE (METHOD OF EHRLICH). (*After Kölliker.*)

The axis-cylinders are stained dark blue. In places the myelin sheath is somewhat stained. The nodes of Ranvier and the divisions of the fibers at some of the nodes are well shown.

were stained after a time, when exposed to the air, an intense-blue color, the other tissue-elements remaining little or not at all affected." It seems clear that, if a solution introduced through blood-vessels can stain the axis-cylinders, the liquid within the latter must be more or less a continuation of that in the blood-vessels. Again, I have suggested that the blood-plasma, including its oxidizing substance, was the liquid in the axis-cylinders; that this is true is shown by Ehrlich's observation that "the conditions in the nerve-structures essential to the methylene-blue reaction" were, he thought (1886): "(1) oxygen saturation; (2) alkalinity." I have shown that these are the essential attributes of blood-plasma.

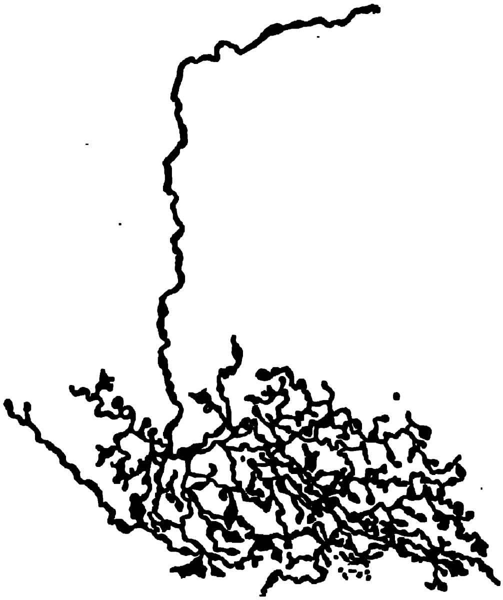

FIG. 2.—SENSORY NERVE-ENDING STAINED WITH METHYLENE-BLUE (METHOD OF EHRLICH) IN THE EXOCARDIUM OF THE LEFT AURICLE OF A GRAY RAT. (*After Smirnow.*)

This seems to me to afford an insight into the physiological chemistry of the axis-cylinder of the neuraxon when a short distance below the latter it has become a medullated nerve. Indeed, the prevailing view that the myelin represents a protective and insulating coat may at least be said to be open to doubt, especially when coupled with the facts that its chemical composition is unknown, and that there is another external coat: the neuro-keratin neurilemma, which suggests, by its composition, that it is an isolating covering and that it also fulfills this rôle in non-medullated nerves. That the myelin is the seat of a combustion process during which heat is liberated and a decomposition product, cholin, is formed, we have seen. If we now consider the composition of the active component of myelin, lecithin, *i.e.*, carbohydrates and phosphorus, and its analogy, as regards carbohydrates, to myosinogen, the probability that it serves as a source of energy, as does the latter when in contact with oxygen, suggests itself. That such is the case, however, is shown by the fact that the contents of the neuraxon or axis-cylinder fulfills the conditions necessary for methylene-blue staining, as laid down by Ehrlich, *i.e.*, oxygen saturation and alkalinity, the characteristics of blood-plasma. Indeed, it seems to me permissible to conclude that:—

1. *Myelin, or the white substance of Schwann, is to nerve-structure what myosinogen is to muscle-fiber:* i.e., *its immanent source of energy.*

2. *The axis-cylinder and the canaliculi derived therefrom are made up of fibrils that serve as channels for blood-plasma.*

3. *A part of this blood-plasma penetrates into the axis-cylinder through Ranvier's nodes.*

4. *Lecithin, a body composed mainly of hydrocarbons and phosphorus, the active constituent of myelin and a prominent component of the electric organ of the ray, when exposed to the action of the oxidizing substance liberates energy:* i.e., *nervous energy.*

Continuing our quotations from Professor Barker's article, I will introduce the various points of comparison which appear to me to sustain my interpretation of Apáthy's neuro-fibrils. "Inside the ganglion-cells a reticulum of fine fibrils derived from the neuro-fibrils in transit can be stained a beautiful deep-violet color by Apáthy's chloride-of-gold method." That the latter method can be considered as similar in action to the methylene-blue method and that the stain follows the same channels and affects the same chemical constituents of the plasma is shown by the following remark of Professor Barker's: "With a little care and a good sample of methylene-blue the *nerve-endings* and the *axis-cylinders* of medullated fibers, with which they are continuous, can be stained in a way far surpassing in constancy and completeness the best results of the uncertain gold-chloride procedure." As the methylene-blue and a modified chloride-of-gold stains were those mainly used by Apáthy, no confusion can occur on this score.

Indeed, if we convert all of Apáthy's neuro-fibrils into minute capillaries, their identity as inherent parts of the general circulation is placed on a solid foundation by the following remark of Professor Barker's: "The doctrine of the fibrillary nature of the axon and unstainable portion of the protoplasm of the nerve-cell has recently received support from the studies of Lugaro[39] and Levi.[40] . The former, too, in his studies of the nerve-cell under pathological conditions—for example, after poisoning with *lead* and *arsenic*—finds that the fibrils may become very distinct in the nerve-cells." That this directly points to the one system through which the morbid changes can occur, *i.e.*, the adrenal system, and that it precisely coincides with the foregoing remarks bearing upon this system, is evident.

The similarity of the neuro-fibril, on the one hand, to the axis-cylinder and its cell-body extensions, on the other, now becomes a normal consequence. "Each neuro-fibril is," Apáthy states, "made up of a large number—near its origin, at any rate —of 'elementary fibrils,' and in the course which it follows elementary fibrillæ are being given off at short intervals until finally the neuro-fibril itself may be reduced to a single elementary fibril." The fibrillary structure of an axis-cylinder is as clearly reproduced here as it can well be; the giving off of fibrils but typifies the irregular distribution of "non-medullated" nerve-fibers, and particularly those of the "sympathetic" system.

All this recalls a structure which appears to me to be intimately connected with the general circulation, the neuraxon and its cellular extensions, and Apáthy's neuro-fibrils—all being considered as component parts of the general vascular system: *i.e.*, Virchow's neuroglia.

The prevailing view concerning the rôle of this structure is that it affords a supporting frame-work for the nervous elements. Both in the white matter and gray matter the medullated nerve-fibers are separated one from the other by a net-work of glia-fibers. In the gray substance, however, the neuroglia, though present in greater abundance, as a rule, than in the white substance, varies considerably, the net-work of fibers being especially thick in certain parts. "The neuroglia is present in greatest abundance in the gray matter immediately surrounding the central canal of the cord and the ventricles of the brain (the ependyma, as it is called)," says Stewart[41]: a suggestive feature in connection with the views submitted in the present chapter. The neuroglia-cells, as is well known, are of two kinds: those provided with mossy processes and those that have smooth extensions. A large number of investigators still consider that the latter represent true processes, and that, by freely anastomosing, they make up the mesh-work which surrounds the nerve-cells and their prolongations. Ranvier, however, after a searching study of the subject, was led to conclude that the smooth processes of these (stellate) glia-cells, were in reality neuroglia-fibers which merely passed through the latter in all directions, without forming part of the cellular structure *per se.* We have seen that Apáthy's neuro-fibrils, when they left the "nerve-cell," also passed *through* the cells after forming a reticulum in the latter: a feature which suggests that Apáthy's neuro-fibril and the neuroglia-fiber may be structurally similar.

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[39] Lugaro: Rivista di patol. nerv. e mentale, vol. i, 1896.

[40] Levi: Rivista di patol. nerv. e ment., vol. i, 1896.

It was formerly thought that neuroglia was a variety of connective tissue, but this view no longer prevails. Indeed, so distinct is the latter from neuroglia that the two structures can be differentiated from each other by the simplest tests; thus, Ranvier and Malassez found that connective tissue placed in cold water was not modified after several days' maceration, whereas neuroglia-fibers were completely destroyed after two or three days. On the other hand, connective tissue was completely destroyed by prolonged boiling in water, while neuroglia was hardly altered under similar conditions. The suggestive relationship between Apáthy's neuro-fibrils and glia-fibers offers some ground for the belief that glia-fibers are also nervous elements. This appears to be sustained by the fact that identical results ensue when nerve-fibers and connective tissue are submitted to the last of the two tests mentioned, the nerve-fiber being merely rendered opaque, while the connective tissue is destroyed. As the latter is gelatinous, its destruction is easily accounted for, but why should the nerve-fiber be rendered opaque? Evidently non-medullated fiber had been used in the test, for medullated fiber is always opaque, while the non-medullated is translucent. I am led to suspect, in view of my belief that the axis-cylinder of a nerve contains blood-plasma, that it is the latter which became opaque during the boiling process. This is an important feature, for it would mean that neuroglia-fibers also contain plasma.

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[41] Stewart: Physiology, p. 671, 1900.

The identity of neuroglia-fibers as plasma-channels becomes emphasized when the morbid effects of poisons upon them and upon their cells are studied. Berkley[42] found the cell-bodies of the *vascular* neuroglia "larger, the protoplasmic extensions" being "thick and knotty and the arms extending *toward neighboring vessels* more prominent than in the normal." This was noted in slides derived from animals submitted to experimental acute alcoholic poisoning. When we consider that alcohol primarily stimulates the adrenal system with great violence and that the neuroglia closely invests the blood-vessels, it seems permissible to surmise that the thickenings and knots are dilations due to the centrifugal pressure of the plasma derived from the capillaries. Especially does this seem probable when the fact that "capillaries, like the intermediary vessels, are tortuous and twisted" is added to the rest of the evidence. And these alterations, besides an "exceeding abundance of the polynuclear leucocytes in and around the cerebral vessels," etc., are not peculiar to alcohol, for Berkley emphasizes the fact—demonstrated for the first time—that the lesions produced "are very similar to the pathological lesions produced by other more virulent soluble poisons": additional proof that the adrenal system underlies the morbid process. Serum-poisoning was also found to cause great swelling of the bodies of the vascular neuroglia, "thick groups of these swollen cells" surrounding "nearly all the vessels of any size in the gray layers." In ricin poisoning Berkley found the cell-bodies "universally much larger than the control," and "apparently swollen, even globular in outline." The extensions were also thicker and more nodular. "Are these elements, which belong to the *lymphatic* apparatus," queries the author, "taking up *detritus* from the degenerating protoplasm of the nerve-cells and becoming engorged?" The conclusion that they belonged to the lymphatic system was reached because they were found to contain *lymph,* which, in the language of Johannes Müller, is "blood without its red corpuscles": *i.e., blood-plasma,* and, of course, its due proportion of oxidizing substance.

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[42] Berkley: Johns Hopkins Hospital Reports, vol. vi, No. 1.

Evidently then, it is the *plasma* found in the capillaries of cellular elements of all organs which, crowded by excessive back-pressure (due to the marked contraction of the central vascular trunks induced by the poisons), causes the endothelial plates or cells constituting the walls of what Berkley terms the "intermediary vessels" to look, using his words, "as if they had been subjected to *severe strain,*" as their even walls have "many irregular *bulges* in their outlines." That the neuroglia-fibers are the channels through which it is transmitted is also suggested by a remark made in connection with the effects on the gemmules, the retention of which, writes Berkley, "clearly shows that the swelling comes *from within* the substance of the stem and pushes the gemmulæ, which are still adherent, *outwardly* and apart."

Does a direct connection between the neuroglia-fibers and the protoplasmic processes of neurons exist, as suggested by the fact that Apáthy's neuro-fibrils are stated by him to penetrate the cell-bodies—provided his fibrils *are* glia-fibers? To establish this upon a firm basis, the thickening, bulging, etc., found by Berkley upon the vascular neuroglia must also be shown to extend to the processes of the neuron.

Golgi has expressed the opinion that the greater part of the nerve-cell—*i.e.,* the entire structure excepting the axis-cylinder—was concerned with its nutrition: a view which met with considerable dissension. Among the opponents of this interpretation was Forel,[48] who contended that the entire cell was simultaneously endowed with nutritional and functional attributes. This conception was defended by Ramón y Cajal, and seems likewise sustained by our analysis, so far. Indeed, we have seen that the axis-cylinder, if my interpretation is sound, is able, through the presence of its coat of myelin and its plasma-containing fibrils, not only to supply chemical—probably nervous—energy, but also to undergo nutritional metabolism. Can we say the same of the cell-body of the neuron?

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[48] **Forel: Archiv für Psychiatrie und Nervenheilkunde, vol. 1887.**

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We have seen that the fibrils penetrate the nerve-cell, and that various poisons, as shown by Lugaro and Levi, cause them to become "very distinct." Referring to the intracellular distribution of the fibrils, Barker says of Apáthy: "He describes the finer peripheral neuro-fibrils as follows: They are seen to enter the cell-body and passing out to the peripheral part of its protoplasm, there to break up into a complicated plexus composed of anastomosing elementary fibrils in the outer chromatic zone. From this peripheral plexus there pass through the 'inner alveolar' zone radial branches to the internal chromatic zone, in which is to be seen another fine plexus of elementary fibrils, which, anastomosing and converging, finally form the single strong motor neuro-fibril, which passes out of the cell through the very center of its pyriform process. In other animals studied by Apáthy there are cells with definite dendrites entirely separate from the axon and in these the cellulipetal neuro-fibrils *enter by way of the dendrites*, ramify and anastomose freely inside the cell-body, and then, reuniting, *take their exit from the cell by way of the axon*. Similar relations exist in the ganglion-cells of the vertebrates which he has studied thus far."

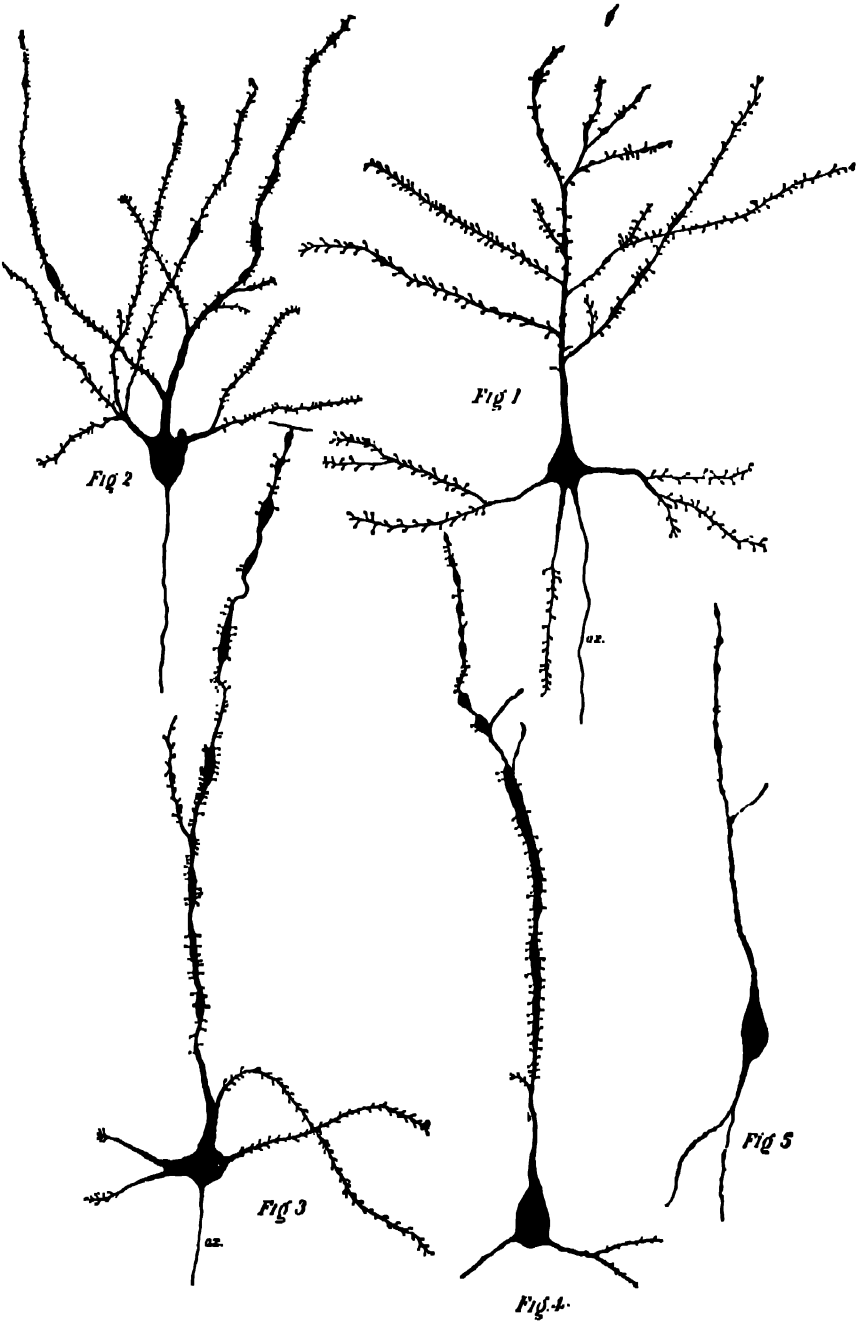
This strikingly coincides with the course of the plasma-fibrils or capillaries as I interpret it. Indeed, if the fibrils enter the cell, form a plexus therein, and pass out "by the way of the axon": fibril, plexus, and axon represent a continuous channel which must contain plasma, since I have ascertained that the axon contains this fluid. Again we obtain a clear indication as regards the path of the blood-stream: it enters by the dendrites and passes out by way of the axon. It is with the dendrites, therefore, that the vascular neuroglia-fibers found thickened, globular, etc., by Berkley in his poisoned animals must be connected. But this fact suggests that these structures should likewise present irregular swellings under the influence of the same agencies, and that the axis-cylinder should show less, the intracellular formation of plexuses and anastomoses interposing a barrier to the too free passage of plasma. That such is actually the case is illustrated by the annexed plates by Berkley, which represent the lesions found in the neurons of the poisoned animals to which reference has been made.

If the protoplasmic processes or dendrites are the first to bear the brunt of the vascular engorgement, the plasma being carried to them through fibrils connected with their tips, these tips or extremities should first show evidence of the expansile pressure. This is well illustrated in Fig. 1, a "*psychical* cell from the second cellular layer of the cortex," which shows, using Berkley's words, "a few pathological tumefactions on the uppermost branches of the apices of the apical dendrite. Otherwise the cell is normal." This cell was selected from a section derived from the brain of an animal poisoned with ricin, death having occurred in thirty-six hours. A feature of importance, however, is that it is the *main*, or apical, dendrite—that giving off the greatest number of subdivisions—which shows the evidences of engorgement; the extremities of the other dendrites are *not* thickened, but they show more or less marked evidences of engorgement as the main trunk is approached. This obviously suggests that the *plasma* penetrates the neuron by way of the main dendrite and that it finds its way into its collaterals cellulipetally; in other words, that, instead of also entering these collateral branches by way of their tips, it is supplied to them by the main trunk—precisely as if it were the main stalk of a plant. Of course, this does not mean that the apices of the collaterals may not subsequently show thickenings; being terminals, they should naturally do so when the pressure exceeds a given limit. This feature is illustrated by Fig. 2, especially by the larger stem of the main trunk. This cell, a projection-cell from the second layer of the cortex, shows the effects of forty-eight hours' ricin poisoning: *i.e.*, of somewhat more prolonged engorgement.

Worthy of special notice, also, is the fact emphasized by Berkley (referring to Fig. 2), that: "there is *now* distinct diminution of the gemmulæ wherever the swellings are found" —which suggests that these minute ball-tipped projections from all collaterals are structurally similar to them, and that, when the engorgement exceeds in centrifugal pressure the resistance of a given area, the walls of the latter, including the gemmules, are more or less flattened out. Suggestive, likewise, is the fact that all the gemmules stand out boldly in both preparations. As many as thirty-six or forty-eight hours having elapsed before death ensued, the animals were evidently submitted to a primary period of intense stimulation, during which the gemmules were overdistended to such an extent as to cause them to lose their retractile property. Indeed, the sudden cessation of adrenal functions and consequent death must have left the cerebral structures much as if the animals had been suddenly killed.

Of marked interest in Fig. 3 is the presence at the extremity of the main, or apical, dendrite of a section of what appears to me to represent a fiber or capillary from which the neuron with which it is connected might have derived its blood-supply. The fact that it crosses its path suggests that the dendrite itself may be a branch of the vessel. Berkley describes this neuron as follows: "Projection-cell of the long apical process variety, showing numbers of large swellings of the protoplasm of the apical dendrite, thinning of the protoplasm of the stems in the interval between the nodules, and considerable loss of the gemmulæ along the margins. The lateral branches have mainly disappeared. The basal processes are retained intact."

The nodules seem to me also to illustrate the process through which the collateral fibers become detached from the main stem, as shown by the denuded cells represented by Figs. 4 and 5. The thinning of the plasma between the stems would account for the manner in which the lateral branches are detached, viz.: when the apical dendrite becomes sufficiently engorged the plasma ceases to circulate in one or more of the nodules, and the intervening protoplasm, failing to be nourished, disintegrates. That the basal processes should be the last to yield in this cell (corresponding in this with the condition of the same stems in Figs. 1 and 2) seems but normal



LESIONS IN THE NEURONS OF ANIMALS AFTER
RICIN POISONING. [Berkley.]

[Johns Hopkins Hospital Reports.]

when we consider their proximity not only to the cell-body, which contains a large supply of fibrils, but also to the axis-cylinder (*ax.* in the drawings), which is the only centrifugal channel through which the engorged plasma can escape.

A feature of the cells shown by Figs. 1, 2, and 3 which strikingly links them to the adrenal phenomena brought on by toxics in the general organism is the fact that, although they are derived from animals in which the doses of ricin injected were reduced with each animal, the morbid phenomena as exemplified by each cell in turn are correspondingly intensified. In other words, the adult rabbit represented by Fig. 1 was given subcutaneously a dose of 0.5 milligramme, and death occurred in thirty-six hours: the cell only shows apical lesions. The second adult rabbit was given the half of the previous dose, *i.e.*, 0.250 milligramme, and death occurred in forty-eight hours: the entire apical dendrite and two of the collaterals are distinctly involved. The third adult rabbit was given the half of the last dose: *i.e.*, 0.125 milligramme, and death occurred in seventy-two hours; the apical dendrite is markedly studded with thickenings, and all but two of its collaterals have disappeared. It is, perhaps, unnecessary to lay stress upon the fact that this is due to the prolongation of the excessive vascular tension: *i.e.*, of the time during which central vascular contraction caused peripheral capillary engorgement. And this need not be ascribed only to ricin. Berkley emphasizes this assertion when he says: "The poison *ricin*, whose action is in many ways *similar to that of many toxalbumins of bacterial source*, is capable of exerting a deep and extensive degenerative influence on the protoplasm of the nerve-cells of the brain." And this may further be extended to other toxics, for he also says: "Poisoning with alcohol in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum, very similar in character to the pathological lesions produced by other more virulent poisons." We thus have evidence in support of my opinion that *poisons capable of causing congestion of the cerebrospinal and other nervous tissues do so by raising the blood-pressure and by thus driving the adrenoxidase-laden plasma into their neuroglia and neurons.* That the alterations in the elements of the neuron should be due to the same centrifugal pressure that prevails in the capillaries of all peripheral structures is obvious. Finally, the fact that phenomena witnessed occur under the influence of congestive poisons affords the complemental evidence in favor of my contention that *a neuron is directly connected with the circulation by one or more of its dendrites, which serve as channels for blood-plasma.*

Even the hæmorrhages brought on by excessive pressure, epistaxis, hæmatemesis, hæmaturia, etc., are exemplified in the engorged neuron shown in Figs. 6 and 7, and also from Berkley's series. The observation of Apáthy's, therefore, that his "cellulipetal neuro-fibrils enter by way of the dendrite, ramify and anastomose freely inside the cell-body, and, then reuniting, take their exit from the cell by way of the axon," finds its application if, as interpreted by myself, *his neuro-fibrils are considered as blood-plasma channels.*

Still, the identity of the fibrils in the cell-body as blood-capillaries has so far only been suggested by the fact that they are continuous with the plasma-containing axis-cylinder and fibrils. While this constitutes strong evidence, the fact that they are blood-channels can only be determined by ascertaining the nature of the process in which the plasma takes part. This may probably be done by inquiring into the composition of a neuron's ground-substance.

THE PHYSIOLOGICAL CHEMISTRY OF THE NEURON.—What is the nature of the ground-substance: *i.e.*, that between the fibrils? After reviewing this subdivision of the general subject Barker says: "A neuron is made up, like all other cells, of nucleus and protoplasm. In the latter a centrosome and an attraction-sphere are present; at least it has been demonstrated in a certain number of nerve-cells. The protoplasmic portion of the cell can be roughly divided into a peripheral exoplasmic portion and a central endoplasmic portion. In neurons, as in muscle-cells, though less distinct in the former than in the latter, there is a tendency to a fibrillary structure, the fibrillæ tending to occur in the peripheral exoplasmic portion of both nerve- and muscle- cells rather than in the endoplasmic portion of the protoplasm. In both exo-

Fig. 6

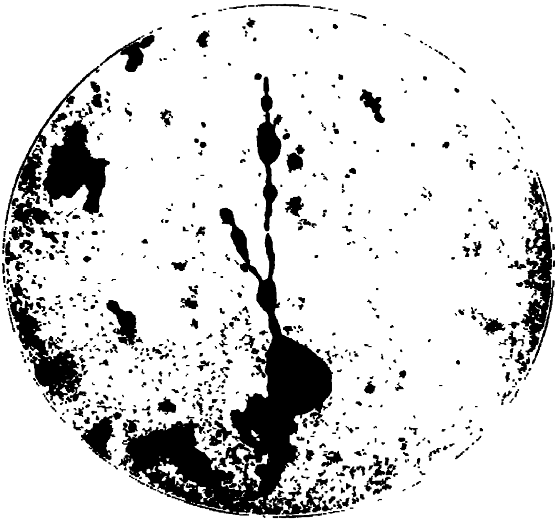
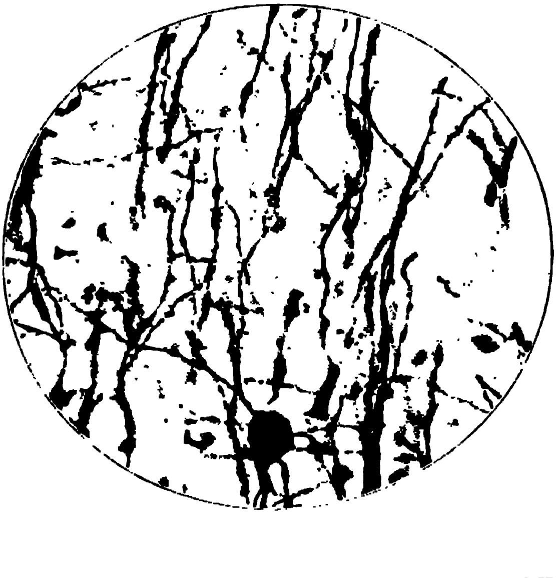


Fig. 7



LESIONS IN THE NEURONS OF ANIMALS AFTER RICIN POISONING. [Berkley.]

[*Johns Hopkins Hospital Reports.*]

plasm and endoplasm there can be made out in tissues which have been fixed *a more or less homogeneous ground-substance* in which are deposited larger and smaller masses of a granular nature. The ground-substance corresponds in tissues fixed with alcohol and stained by the methods of Nissl and Held to the 'unstainable substance' of Nissl, and the masses of granules to the 'stainable substance' of Nissl and the pigment.

"The 'stainable substance' of Nissl in healthy animals of the same age and species, with the same method of fixing and staining, is tolerably constant in appearance and arrangement in the *cell-bodies and dendrites* of the same group of nerve-cells: a fact of extreme importance for nerve-anatomy and pathology. The axons appear to be entirely devoid of the 'stainable substance' of Nissl. Whether the stainable substances represent bodies precipitated from solution through the action of reagents or bodies pre-existent, though invisible, first brought into view through the action of fixing or staining reagents in the hardened tissues, in either case they appear to yield the chemical tests *characteristic of the group of nucleo-albumins.* Whether the staining reaction characteristic of the stainable substance depends upon chemical relations or upon purely physical conditions must, for the present, remain undecided.

"The 'unstainable portion' of the cell-body,—that is, the ground-substance,—though probably functionally much more important than the stainable, is not so well understood; its nature and structure are still as obscure as those of protoplasm in general." Still, the link with features previously brought out by our analysis now seems within reach.

Held has maintained that the stainable Nissl bodies represent simply substances precipitated from solution by the action of fixing mixtures; Fischer was led to the same conclusion. Barker says, in this connection, that he repeatedly convinced himself of the *homogeneous* appearance of the protoplasm of the nerve-cell when it is examined immediately after the removal from the living body. That the ground-substance is homogeneous, and that the unstainable portion is a product of dissociation of some of its constituents, are therefore probable. But the stainable portion we have seen has yielded the chemical tests "characteristic of the group of nucleo-albumins." We are not, therefore, dealing with the group of nitrogenous fats to which lecithin, the main constituent of myelin, belongs, but with what probably represents, not a mere artifact, but an individual constituent which is precipitated by the fixing mixtures. It is important to determine, therefore, the exact nature of the Nissl "bodies," and perhaps by a process of exclusion ascertain that of the unstainable substance.

"Held," says Professor Barker, "undertook a most careful and exact chemical study of the granules in alcohol tissues. Thus, he found that the Nissl bodies are insoluble in dilute and concentrated mineral acids, in acetic acid, boiling alcohol, cold or boiling ether, and in chloroform. On the other hand, they are easily soluble in dilute and concentrated alkalies. With pepsin and hydrochloric-acid digestion he found that the ground-mass of the protoplasm vanished and that the Nissl bodies alone remained undigested: the reverse of what occurred on treatment with an alkali. The Nissl bodies yielded no reaction with Millon's or Adamkiewicz's reagent. Held obtained, however, slightly positive results with Lilienfeld and Monti's microchemical test for phosphorus, and a considerable quantity of the gray matter of the spinal marrow after digestion with pepsin and hydrochloric acid examined by Siegfried, of the physiological laboratory of Leipzig, showed the presence of phosphorus. Held concludes, however, from these various reactions, that the Nissl bodies belong to the group of the nucleo-albumins: a view which agrees with the investigations of Halliburton, who found in the gray matter a nucleo-albumin which coagulated at from 55° to 60° C. and which contained *as much as 0.5 per cent. of phosphorus.*"

The large proportion of phosphorus further sustains the preponderating rôle that the oxygen of the plasma must play in the neuron, owing to the activity of the reaction between these two elements. It also indicates a close relationship between the neuron and all other cellular structures of the organism. Thus, referring to Held, Barker says: "He asserts that in numerous experiments with his method (formol freezing) he has found in the *most different organs* constituents of the cell-body which behave not only tinctorially, but also morhologically, *exactly* as the *stainable substance* in nerve-cells. He described them in *gland*-cells, *liver*-cells, in cells of the *ncreas,* in the cells of some sarcomatous tumors, in certain *onnective-tissue cells,* but especially in normal and pathological *ymph-glands.* Cajal[44] also asserts that the stainable substance of Nissl is not specific for the nerve-cells, as he has demonstrated its presence in certain of the *leucocytes* and of the *connective-tissue elements.*" Nissl's bodies appear to me, therefore, as constituting an organized component of the ground-substance of the neuron, a nucleo-albumin rich in phosphorus, which, judging from its similarity to a large number of cellular structures elsewhere in the organism, *represents the cell-structure itself,* precisely as is the hepatic cell when free from glycogen, bile, or the agencies from which these are derived. It is to the neuron what the neurilemma, Mauthner's sheath, etc., are to the internodal segment of a nerve, and includes—as does the protoplasmic membrane of Schwann—the nucleolated nucleus.

The unstainable portion must be the equivalent of myelin: the white substance of Schwann. We have seen that this is also unstainable. Even picrocarmine does not stain it, and Ranvier states that the axis-cylinder becomes stained at the nodes because there is no myelin in this region of the nerve. The similarity between myelin of the nerves and that of the cerebro-spinal system is emphasized by Foster when he says: "Obviously the fat of the white matter of the *central* nervous system and of spinal *nerves* (of which fat by far the greater part must exist in the medulla, and for nearly the whole of the medulla) is a very complex body indeed, especially so if the cholesterin exists in combination with the lecithin, or cerebrin (or protagon). Being so complex, it is naturally very unstable, and, indeed, in its stability resembles proteid matter." This also suggests, however, that protagon, a nitrogenous body containing phosphorus isolated by Liebreich from brain-substance, may be the unstainable substance we are seeking. Hoppe-Seyler and Diakonoff, having found it to be composed of lecithin and cerebrin, the direct connection with the former is not removed. Protagon readily breaks up into its constituents. Howell states that, "while protagon seems to be regarded as the principal form in which lecithin occurs in the brain, simple lecithin is believed to be present in the nerves and other organs," and he refers to Noll,[45] who found "the quantity of protagon in the spinal cord may amount to 25 per cent. of the dry solids; in the brain, to 22 per cent.; and in the sciatic nerve, to 7.5 per cent." That it is difficult to analyze this question is suggested by his closing remark: "Regarding the synthesis of lecithin in the body, or the physiological importance of the substance, nothing is known." We have seen the important rôle that it probably plays as myelin; its presence in such large quantities, as a constituent of protagon, in the cerebro-spinal system plainly points to it as of the unstainable ground-substance of the neuron.

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[44] Cajal: Revista trimest. micrografica, vol. 1, No. 1, March, 1896.

What is the rôle of cerebrin, which, with lecithin, forms protagon, and from which it is readily separated? In a study of the chemistry of nerve-degeneration Halliburton and Mott[46] refer to the fact that they had previously shown that in general paralysis of the insane "the marked degeneration that occurs in the brain is accompanied by the passing of products of degeneration into the spinal fluid. Of these," says the authors, "nucleo-proteid and cholin are those which can be most readily detected. Cholin can also be found in the blood." Having continued this work, they now find "that this is not peculiar to the disease just mentioned, but that in various other degenerative nervous diseases (combined sclerosis, disseminated sclerosis, alcoholic neuritis, beriberi) cholin can be also detected in the blood." The tests that they employed were mainly two: (1) "the obtaining of the characteristic octahedral crystals of the platinum double salt from the alcoholic extract of the blood"; (2) a physiological test—and a very interesting one, I may add, if the functions of the adrenal system are included in the process, namely: "the lowering of blood-pressure," which the authors consider as "partly cardiac in origin and partly due to dilation of peripheral vessels," and

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[45] Noll: Zeitschrift für physiol. Chemie, Bd. xxvii, S. 370, 1899.

[46] Halliburton and Mott: Journal of Physiology, Feb. 28, 1901.

"which a saline solution of the residue of the alcoholic extract produces." This fall "is abolished," they further state, "if the animal has been atropinized." I may incidentally remark that these few lines embody the pathogenesis of most neuroses attended with degeneration, viewed from my standpoint, since we have here the phenomena incident upon arrest of function, auto-intoxication, and toxic suprarenal insufficiency. But directly bearing upon the subject in point is the evident identity of cholin as a product of degeneration. It "has its source in lecithin decomposition and putrefaction," says Howell. But it is likewise, as we have seen, a waste-product of normal nervous-tissue metabolism, being eliminated with the bile in a modified form. That *cerebrin is also a product of putrefaction and of physiological metabolism* is suggested by two facts: it is found in pus-corpuscles and its formula and that of cholin present considerable analogy. Even taking as standard that furnished by H. Müller, which has given rise to considerable controversy, cerebrin is $C_{17}H_{33}NO_3$, while cholin is $C_5H_{15}NO_2$. *Lecithin, therefore, becomes the functional ground-substance of the cell-body of the neuron, just as it is in the nerve. Both in the neuron and its continuation, the nerve, therefore, the vascular fibrils carry blood-plasma, which, by passing through their walls, maintains a continuous reaction, of which the phosphorus of the lecithin and the oxygen of the blood-plasma are main reagents and chemical energy the end-result.* The relationship between the vascular fibrils and the ground-substance, nucleus, etc., is well shown in the engraving on page 558.

But lecithin, though a useful product of metabolism, requires in its formation the aid of protoplasmic function, as does, in the muscle, the elaboration of myosinogen. In the cell-body this is probably performed, we have seen, by structures which the Nissl bodies, as nucleo-albumins, represent. Indeed, in a study of the action of fixatives upon *protoplasm* Hardy found[47] that, "when a soluble colloid is fixed by the action of a fixing reagent, it acquires a comparatively coarse structure in the process, which differs wholly or in part from the structure of the soluble colloid." Again, that these protoplasmic

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[47] Hardy: Journal of Physiology, May 11, 1899.

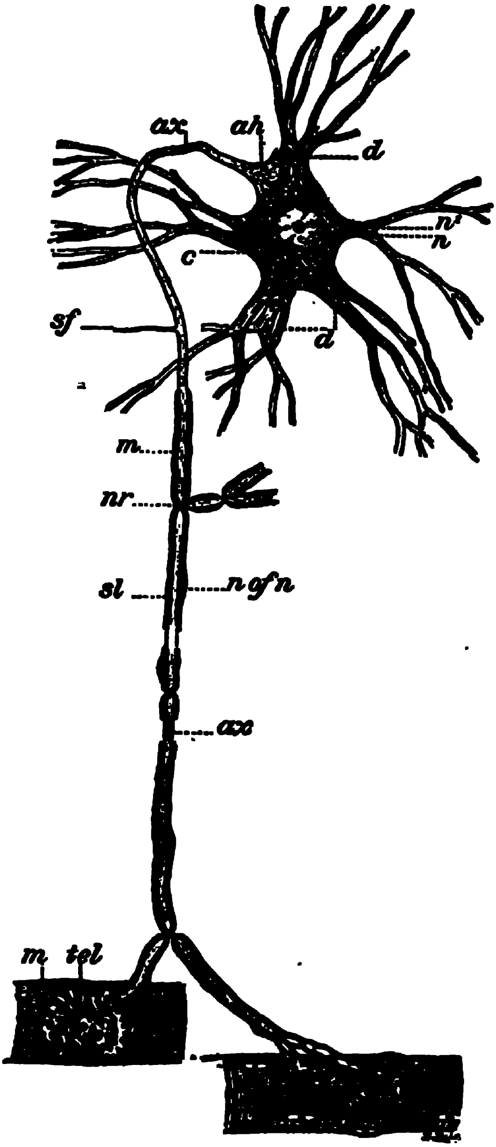

FIG. 3.—SCHEMATIC REPRESENTATION OF THE LOWER MOTOR NEURON.

The motor cell from the ventral horn of the spinal cord, together with all its protoplasmic processes and their divisions, its axis-cylinder process with its divisions, side-fibrils or collaterals, and end-ramifications (telodendrions, or motor end-plates) in the muscle represent parts of a single cell or *neuron*. *n'*, Nucleolus. *c*, Cytoplasm showing the dark colored Nissl bodies and lighter ground-substance. *d*, Protoplasmic processes (dendrites) containing Nissl bodies. (*Barker*.)

structures are supplied by a vascular net-work similar to that of other cellular structures is shown by the observations of Apáthy, who took them for nerve-fibrils. Barker, referring to this feature of his investigations, says: "As to the relations of the neuro-fibrils to sensory surfaces, on the one hand, and muscular tissue, on the other, Apáthy makes very definite statements, especially in the last chapter of his article. A neuro-fibril entering the cytoplasm of an epithelial cell of a sensory surface in the leech breaks up (very much as in a ganglion-cell) into a *finer reticulum* composed of the *elementary fibrils*. A large number of the constituent fibrils, however, perhaps the majority, leave the cell in order to take part in the formation of a complicated *interepithelial fibril-plexus*." Neuron and nerve, therefore, appear to be similar to other organs as functional entities and to be subject to the same laws, including the circulation through them of adrenoxidase.

This explains for the first time why tetanotoxin was found in the nerves by Bruschettini, Marie and others and why, in fact, as shown by Marie and Morax (see p. 1441), tetanotoxin, injected into the tissues, enters and ascends the axis-cylinders of nerves—an observation confirmed by Meyer and Ransom.

The rôle of the blood-plasma seems so clearly defined in the foregoing analysis that I deem it permissible to conclude that *all parts of a neuron—cell-body, dendrites, neuraxon or axis-cylinder—are channels for adrenoxidase-laden blood-plasma.*

Since I thus pointed out in 1903, that the adrenal secretion, converted into adrenoxidase, circulated in the nerves and nerve-cells, Lichwitz[47a] found that in the frog "adrenalin traveled from the lower extremities to the upper, when these were only connected by nerves," thus confirming my observation.

Are dendrites provided, as are the cell-body and the axis-cylinder, with myelin? We have seen that, as stated by Barker, "the stainable substance of Nissl in healthy animals of the same age and species, with the same method of fixing and staining, is tolerably constant in appearance and arrangement in the *cell-bodies and dendrites* of the same group of nerve-cells." He also states that "the axons appear to be entirely devoid of the stainable substance of Nissl"; but Berkley,[48] referring to the nerve-fiber terminals which are extensions of the axon, writes: "The researches of Flechsig, as well as my own, have shown that these fine branches are furnished with a thin *layer of myelin* nearly to their termination." As this refers to intracerebral nerve-fibers, I am brought to conclude that *the entire nervous system is built upon the same plan:* i.e., *of fibrils containing blood-plasma, surrounded by a layer of myelin. The main constituents of these bodies, the oxygen of the plasma and the phosphorus of the myelin, are thus brought into contact, and nervous energy is liberated.*

[47a] Lichwitz: Arch. f. exper. Path. u. Pharm., March 9, 1908.
[48] Berkley: Johns Hopkins Hospital Reports, vol. vi, p. 89, 1897.

All this seems to me confirmed by the manner in which many, now paradoxical, phenomena are accounted for:—

The production of nervous energy, not only by the neuron, but also by the neural myelin, confirms the "avalanche" theory of Pflüger, which, though at first combated by Marey, was sustained by the latter after a series of experiments. Pflüger held that nervous excitation increased along the length of motor nerves: á view which strongly sustains my conclusion. Richet found also that excitation of a sensory nerve was more intense when transmitted from the periphery than when excitation was applied to a part of the nerve nearer to its center (Duval). It is evident, therefore, that an accumulation of energy takes place in sensory as well as in motor nerves.

My views are also sustained by the evidence afforded by nerve-degeneration. Quoting Turck's conception, Professor Barker refers to the Wallerian doctrine as follows: "Converting the Wallerian doctrine into terms of the neuron concept, the following law may be laid down: When it has suffered a solution of continuity, severing its connection with the cell-body and dendrites of the neuron to which it belongs, the axon, together with the myelin sheath covering it, undergoes in the part distal to the lesion acute and complete degeneration. This degeneration includes, not only the main axon, but also its terminals, together with the collaterals and their terminals connected with it."

If the gradual increase of energy along the nerve, or "avalanche" just referred to, is considered as a factor of the function and the sum-total of the energy utilized and is interpreted as made up of *neuron energy plus gradually increased nerve-energy,* the following main facts connected with nerve-degeneration seem to me to find their explanation:—

Section of a motor nerve will cause degeneration of the peripheral fragment, and atrophy of the muscles supplied by it. I have emphasized the functional importance of a continuous supply of nervous energy, both upon the vascular and cellular elements of any organ.

There is no degeneration of the upper, or proximal, fragment, however, except as far as the first Ranvier node. This has been ascribed to traumatism, but we can readily understand now that section through an internodal segment destroys the mechanism of that segment, the supply of oxidizing substance failing to reach the myelin through the fibrils and their canaliculi. Its nutritional or "passive" function is thus arrested.

That the nerve and even its neuron require some of their own energy to permanently sustain their own life, as emphasized by Marinesco,[49] especially when long stretches of nerve are involved, is shown by the fact that if the seat of its ultimate distribution is destroyed,—a muscle, for instance,—or if it is disconnected from the latter, the nerve may, as sometimes occurs after amputations and peripheral neuritis, degenerate, and the process extend up to and include the cornual cell. That this does not always occur is doubtless due to the fact that the subdivisions of a nerve all contribute to the maintenance of its life, and that the chances that degeneration of a long nerve will occur are proportionate to the number of branches it supplies in its course.

The sensory nerves show the same attributes, but, of course, in a reversed direction. Section of the posterior root above a ganglion is followed by degeneration of the dorsal stump, which may include the extension into the cord. Amputation sometimes causes not only atrophy of the peripheral fibers, but also of the ganglion-cells and their prolongations in the columns. "The living muscle seems so organized that without nervous stimulation it can no more live than can the tropical animal without warmth or the rose without water," says Morel. How true this is is emphasized by the precaution Nature takes to nourish the nerve throughout its entire length and thus to insure the conversion of the chemical energy contained in its myelin and the plasma into nervous energy.

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[49] Marinesco: Neurol. Centralbl., Bd. xi, 1892.

THE MINUTE CIRCULATION OF THE CEREBRO-SPINAL SUBSTANCE.—Such a circulation as that I suggest by this title is not thought to exist. Both in the central ganglionic and in the cortical arterial systems the arteries are now believed to be "terminal": *i.e.,* to neither supply nor receive any anastomotic branch. They penetrate the cerebral substance to terminate there. The veins are similarly disposed. Deprived of valves and muscular tissue, they are likewise considered as "terminal" in the sense attributed to that word in respect to the arteries: a normal outcome of the absence of connection with the latter as supposedly indicated by the impediment presented to the injection of fluids in them. And yet, how does the blood, with its corpuscles, find its way from the arteries to the veins? Does it filtrate through the arterial walls, find its way through the lymph-spaces to the venous walls, and reach the sinuses? Of course, we have elsewhere in the organism both the effusion of plasma and the emigration of corpuscles through vascular walls; but this is a process of a different kind, and for which the blood-stream only plays the part of purveyor; it represents the main factor of a reparative and protective function, of which, indeed, the cerebro-spinal system is a prominent beneficiary when need be. There is a wide margin, however, between this process and the mechanism of circulation, which includes channels beginning at the heart and ending in this organ, and having for its purpose, not only to carry oxygen to all parts of the organism, but also to rapidly remove blood as fast as its oxygen-ratio is being reduced. "Terminal" vessels do not satisfy this *sine qua non* of perfect metabolism in the cerebro-spinal system, notwithstanding the presence in the superficial structures of more or less close capillary net-works. Indeed, the very presence of these capillaries seems to me to point to these deeper "terminals" as incongruities.

The marked evidences of engorgement so typically shown by Berkley's illustrations, and to which I have referred, are characterized by a suggestive feature: *i.e.*, they occur, as far as the neuroglia is concerned, in the elements adjoining the blood-vessels or connected with them. Thus, Berkley writes: "In the silver slides the support elements proper, so far as the stain shows, present *no variations from the control*, but, on the other hand, the *vascular* neuroglia gives indication that alterations are taking place within its structures, and show considerable variations from control preparations. The cell-bodies are larger, the protoplasmic extensions are thick and knotty, and the arms extending *toward neighboring vessels* are more prominent than in the normal." As "the capillaries, like the intermediary vessels, are tortuous and twisted,"—evidences of intense engorgement, further emphasized by the "closely packed" white blood-corpuscles found in the vascular lumen, —it seems but logical that the engorged capillary and the engorged neuroglia-fibers should be continuous; otherwise the latter neuroglia swelling would remain unaccounted for.

Referring to the spinal cord, Berdal[50] states that "the moment the blood-vessels penetrate into the cord they become covered, on a level with the perimedullary neuroglia layer, with a coating of neuroglia, which follows them throughout *all* their ramifications and accompanies them along their *entire* course." Such a coating over cerebral capillaries would readily account for the engorgement of both structures to which we have just referred, since the channel, notwithstanding the alteration in its external aspect owing to the assumption of an extra coat, would, after all, be continuous. That such is the case is sustained by the fact that in what has been termed "chronic ependymitis"—doubtless a condition in which the layer of neuroglia becomes permanently engorged—a marked thickening of the tissue occurs (O. Israel). The increase of blood in the neuroglia-fibers which this morbid condition involves not only coincides with the swellings observed by Berkley after various forms of poisoning, but it is accounted for by the fact that ependymal neuroglia-cells were found by Marchi to send "a central extension which penetrates into the optic thalamus, where it subdivides to become *fixed upon the walls of the blood-*

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[50] Berdal: *Loc. cit.*, p. 192.

vessels" (Berdal). This recalls the interesting feature in Fig. 3 of the plate opposite page 550. In the projection-cell represented the extremity of the long and irregularly-swollen apical process is also connected with the wall of what must be a diminutive blood-channel, if plasma is at all the cause of the cellular engorgement. Again, the neuroglia-cell, shown below, copied from an article by Andriezen, to which I will presently refer,[51] may be seen to be directly attached to a vessel. Indeed, we have Golgi's own testimony to the effect that some of the protoplasmic extensions of the nerve-cell are attached to neuroglia-fibers and to blood-vessels.

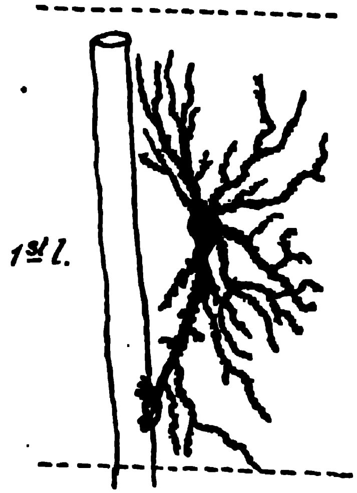

FIG. 1.—"A PROTOPLASMIC GLIA-CELL FROM A HUMAN BRAIN (FIRST LAYER OF CORTEX)." (*Andriezen.*)

The manner in which the neuroglia-cells and their fibers are connected with blood-vessels suggests that they are essentially different structurally, the neuroglia-elements being, not branches or subdivisions of the vascular system, but nervous structures which, at a given time during embryological development, became affixed to the vascular walls. This is sustained by the fact that neuroglia is, like all nervous elements, of epiblastic origin. Again, there is considerable analogy between nerve- and neuroglia- fibers. Foster emphasizes this fact when he says: "Since the nerve-filaments, like the neuroglia-fibers, are very fine, and take, like them, an irregular course, it often becomes very difficult in a section to determine exactly which is neuroglia and which are nervous elements."

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[51] Andriezen: Brain, Winter, 1894.

What is the rôle of the neuroglia and how is it functionally related to the true nervous elements? Suggestive, in this connection, are the following lines of Professor Foster's: "A medullated nerve-fiber of the white matter of the spinal cord resembles a medullated nerve-fiber of a nerve in being composed of an axis-cylinder and a medulla; but it possesses no primitive sheath or neurilemma. This is absent, and, indeed, is not wanted; *the tubular sheath of neuroglia* affords, in the spinal cord (and, as we shall see, in the *central nervous system generally*), the support which in nerves is afforded *by the neurilemma.*"[62] This shows conclusively that for a certain distance, at least, the neuroglia-sheath and the myelin act as coats for the one axis-cylinder: *i.e.*, for the fibrils containing blood-plasma. But we have seen that myelin is not the passive insulating substance that it is now thought to be; if my views are sound, it represents one of the two most important factors of nerve-composition, and, indeed, the main source of nervous energy. In modifying the accepted view concerning its functions, however, I have eliminated its rôle as insulating layer, leaving nothing but the neurilemma, or external, tubular investing sheath, for the protection and insulation of the "battery elements," as it were, the myelin and its oxidizing plasma. It is, therefore, this protective and insulating sheath that the neuroglia replaces in the white substance of the cord and in "the central nervous system generally": *i.e.*, wherever the myelin and its inclosed blood-plasma are present in the cerebro-spinal axis.

We have seen that, according to Barker, and as shown by the researches of Flechsig and Berkley, the dendrites of neurons are furnished with a thin layer of myelin nearly to their termination; while I have shown,—conclusively, I now believe—that their central canal contains blood-plasma. We have precisely, therefore, the structure of a nerve, minus its neurilemma. Indeed, the similarity even extends to the subdivision of the dendritic central canal into fibrils, for Berdal says, referring to the dendrites: "These prolongations seem striated longitudinally as is the cell, and appear to be composed of fascicles of fibrils which are continuous with those of the cellular body." A single structure is missing, however, that which, we have just seen, is represented by the neuroglia in cerebrospinal nervous elements: *i.e.*, the neurilemma. Obviously, the absence of a protective insulating sheath around the cell-body of the neuron and its extensions, considering their functional importance as generators of nervous energy, becomes absolutely incompatible with existing conditions, since the myelin would thus be exposed externally. Indeed, that the cell-body and its dendrites are supplied with an external sheath is shown by the following lines of Berkley's[58]: "Around the body of the cell we find an insulating mass of fluid contained in the pericellular lymph-sac, and as a capsule to the sac there appears a slight condensation of the tissue at this point that would take the place of a retaining membrane. This membrane apparently terminates where the first of the gemmulæ are thrown off from the ascending portion of the primordial process, and likewise at the location where the first buds appear on the basal dendrites. Does the insulating fluid and covering really end at this point? In absolute-alcohol sections of the cortex of the cerebellum taken parallel with the surface and stained with the anilines, particularly the blue-black, it is *quite readily demonstrable* that the thin membrane, which is now *undoubtedly composed of fine glia-filaments,* does not really cease at this point, but becomes attenuated, and continues to ascend *and cover the protoplasmic prolongations* of the cell." This plainly shows that *the cell-body of the neuron and its dendrites are supplied with a covering which is to them what the neurilemma is to nerve-fibers; this covering is similar to that investing these nerve-fibers:* i.e., *a sheath of neuroglia.*

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[62] All italics are my own.

This only affords, however, information concerning the neuroglia supplied to the neuron *per se,* and to the structures which the axons become a short distance below the cell: *i.e.,* nerves. But we have still to study an important question: *i.e.*, the identity of the intermediary fibrils of neuroglia—important in the sense that it has a certain bearing upon the concordance between the older views of Gerlach and the modern observations and conclusions of Golgi. Indeed, if the entire cerebrospinal axis is made up (as far as true nervous elements go) of these medullated glia-covered nerve-fibers and dendrites, we may well conclude with Gerlach that nerve-cells are united by an intricate net-work of extremely delicate nerve-fibrils. If, on the other hand, the cell-body, its dendrites, and its axon are alone medullated and glia- or neurilemma- covered, the connection *with the vascular system* being established by *non-medullated fibrils,* I am in accord with Golgi, who denies the existence of any connection through nervous structures between neurons.

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[58] Berkley: *Loc. cit.,* pages 90 and 91.

That Golgi's view prevails is suggested—provided my own view that fibrils are plasma-channels is accepted—by the following lines by Professor Foster: "The larger part of the gray matter consists, besides a neuroglia supporting the nervous elements, of *nerve-filaments* running in various directions and forming, not a plexus properly so called, but an interlacement of extreme complexity." If the italicized words "nerve-filaments" are converted, in accordance with my view, into *neuroglia-fibrils,* the rest of the quotation will lead us to the solution of the question: "These filaments are, on the one hand, the fine *medullated* fibers spoken of above as being recognized with difficulty, and, on the other hand, *non-medullated* filaments ranging from fairly wide and conspicuous naked axis-cylinders down to fibrils of *extreme tenuity,* the latter arising apparently either from the division of axis-cylinders and nerve-fibers passing into or out of the gray matter or from the continued *branching of the nerve-cells.*"

The solution, it seems to me, lies in the fact that non-medullated fibrils exist at all, and that these range from fairly wide *axis-cylinders* down to fibrils of extreme tenuity, some of which, at least, appear to originate from dendrites. Indeed, this indicates that these non-medullated fibrils (of neuroglia, as stated by Berkley) represent the continuation of the main, or apical, dendrite (or dendrites, for there are often more than one). Since these neuroglia-fibers are deprived of myelin, they cannot serve as sources of nervous energy, and merely represent, therefore, delicate channels through which blood-plasma, obtained by them directly or indirectly from a so-called "terminal" capillary, finds its way to the apical, or main, dendrite. The conclusion which this imposes seems to me self-evident: *A neuron is an autonomous organ as a source of nervous energy, and is supplied with blood-plasma through non-medullated neuroglia-fibrils, which are continuous with the external covering of its apical dendrites.*

Are Apáthy's fibrils, which, in the leech and earthworm, were found by him to penetrate the cell-bodies of neurons, the neuroglia-fibrils just studied? Gerlach, Haller, and others have also referred to the existence of delicate nervous net-works connected with the cells. The mere transformation of these fibrils into plasma-channels has enabled me, we have just seen, to link them with all the other elements of the function studied. In other words, I simply converted the fibrils into neuroglia blood-channels and found them to satisfy the requirements of the latter. Apáthy found that a neuro-fibril passed out of "a process of a nerve-cell": there is no fibril other than the neuroglia-fiber that is continuous with the apical dendrite that this neuro-fibril could represent. The neuro-fibril was found by Apáthy to be composed of "elementary fibrils": we have seen that this is precisely the arrangement within the neuroglia-fibers. He states that in their course "elementary fibrillæ are being given off at short intervals, until finally the neuro-fibril itself may be reduced to a single elementary fibril": I have quoted the statement of Professor Foster's that, as regards the "fibrils of extreme tenuity,"—those, we found to act as neuroglia neurilemma,—they arose "apparently from the division of axis-cylinders." Finally, the neuro-fibrils, after freely anastomosing in the cell-body (having entered by way of the dendrite), are stated "to take their exit by way of the axon." This seems to me to indicate clearly, in addition to the evidence adduced in the foregoing pages, that *Apáthy's neuro-fibrils and the various net-works thought to be composed of nerve-fibers by Gerlach, Golgi, B. Haller, and others represent the one and same system of neuroglia-fibrils, some of which* *contain myelin and blood-plasma and may, therefore, be considered as nerves, while others only contain plasma and are, therefore, blood-channels.*

Under these circumstances, are the above-mentioned investigators not justified in considering the net-works referred to as nervous structures? They would be justified in doing so, did *all* the neuroglia-fibrils contain myelin; but it is the *absence* of this compound in the fibrils that serve as channels for plasma between blood-vessels and the apical dendrites of the neuron which seems to me to neutralize their view. Were there any evidence that a medullated fiber of any kind connects any portion of the cell with another structure capable of converting chemical energy into nervous energy, the question would remain an open one; but such is not the case; the absence of myelin in the neuroglia-fibrils connecting the neuron with the source of its blood-supply seems to point distinctly to the need of its absolute isolation, not only to avoid the promiscuous dispersion of the nervous energy it is able to produce, but also to enable it to store this energy and to direct it in the physiological paths.

The presence of the non-medullated fibers among the cerebro-spinal nervous elements becomes evident when the structural difference between the gray matter and the white matter is interpreted from the standpoint of my view. "Owing to the relative abundance of white refractive medulla," says Professor Foster, "the white matter possesses in fresh specimens a characteristic *opaque* white color; hence the name." . . . "In transverse sections of the cord *nearly the whole* of the white matter appears, under the microscope, to be composed of minute circles, the transverse sections of the longitudinally-disposed fibers." . . . "The *gray* matter, from the relative *scantiness of medulla,* has no such opaque-whiteness, is much more *translucent,* and, in fresh specimens, has a gray or rather *pinkish*-gray color, the reddish tint being due to the presence partly of pigment and partly of blood, for the *blood-vessels* are much more abundant in the gray matter than in the white." That in the cerebral cortex, for instance, these vessels should represent the starting-point of the neuroglia non-medullary fibrils needs hardly to be emphasized. They are now termed "terminal," but their appearance as such is readily accounted for by the fact that here, as in the cord, they are said to be imbedded in neuroglia, whereas, in reality, the latter, composed, as it is, of a mass of diminutive fibrils, is directly *affixed* to the vessel, acting precisely as would a multitude of minute subdivisions of the vessel itself. Each fibril (in which the blood-stream is so slender that it only appears "pinkish" through its translucent covering) is, in fact, a composite counterpart of the ependymal fibril and other neuroglia structures to which I have referred. In other words, *each neuroglia-fibril is affixed to the wall of the vessel either directly or through the intermediary of a neuroglia-cell, and therefrom extends to the main, or apical, dendrite, or dendrites, of some neuron.* In addition, however, this enables me to conclude that *a neuron receives its nutrition and its oxidizing substance directly from the general circulation,* and that *the blood which enters by way of the apical dendrites is distributed to the free dendrites and to the cell-body.*

A question suggests itself in this connection, however, viz.: How does the blood in the collaterals return to the main dendrite to find its way with the latter's blood into the cell-body? This appears to me to find its explanation in the following (already quoted) sentence, in which Berkley describes the cell-body: "Around the body of the cell we find an insulating mass of *fluid* contained in the *pericellular lymph-sac,* and as a capsule to the sac there appears a slight condensation of the tissue at this point, that would take the place of a *retaining membrane.*" The retaining membrane is doubtless the neuroglia covering of the collateral, as it is of the entire cell; underneath, therefore, is the lymph-sac—which I consider as a plasma-sac. But we have seen that Flechsig and Berkley's researches have shown that these "fine branches are furnished with a thin layer of myelin nearly to their termination." That this myelin must, as elsewhere, be supported by the neuroglia covering and in contact with it is evident: a feature which relegates the plasma toward the center, though in contact with the myelin. If we now recall the fact that fibrils have also been discerned even in these delicate collaterals, it becomes a question whether they serve to transmit plasma, centrifugally or centripetally. As

Berkley's experiments have shown that they become the seat of swellings under the influence of poisons, there must be no escape for fluids through their walls; indeed, gemmulation would become impossible were the centrifugal pressure necessary counteracted by the escape of the plasma into lymph-spaces. That the blood returns toward the cell-body and through some of the central fibrils is therefore probable. Under these conditions I can submit, as a working proposition, that *the plasma which enters the collaterals is returned to the apical dendrite, and to the cell-body with the blood of the latter. The blood of the cell-body then passes out through the axon.*

How does the blood leave the axon of the neuron in the substance of the brain and cord? This question plainly resolves itself into the following: How does the blood reach the veins from the axon? "The perivascular lymphatics . . . are especially found in connection with the vessels of the brain" says Gray[54]; "these vessels are inclosed in a sheath which acts as a lymphatic channel, through which the lymph is carried to the subarachnoid and subdural spaces, from which it is returned to the general circulation." This familiar fact would be unexplainable after the views I have advanced concerning the circulation of arterial blood were the return of blood to the veins not the purpose of the lymphatic *sheaths,* for the same authority states that lymphatic *vessels* "have not at present [1901] been demonstrated in the dura mater or the substance of the brain." Again, when we consider that *perineural,* as well as *perivascular,* spaces exist, we are brought to realize that by linking the axon of a neuron to a venule, with a lymphatic space as intermediary, we have the elements of a mechanism which not only utilizes structures that are *known* to be present in the cerebro-spinal axis, but which also satisfy the needs of the function. Finally, if an axon is itself buried (up to the neck of its bulbous terminals) in a perineural sheath, which in turn communicates with a vein through stomata, as is the case in nerves, the blood of the axon is provided with a clear path to the general blood-stream.

That the blood of the neuron is eliminated as it is in other nervous structures—*via* the axon—is evident; but do lymph-spaces connected with *veins* actually receive this blood? Referring to the effects of acute alcoholic poisoning upon the veins, Berkley says: "Changes in the coats of these vessels are similar to those in the arterial system, but aggregations of dying polynuclear corpuscles are more frequent, and are by far the most striking feature both of their contents and surroundings. These aggregations, which may vary from three or four to a dozen or more, are located both *within* and *without* the lumen of the vessel (especially the smaller ones). Within the lumen are collections of white corpuscles filling the interior, and numbers are seen *penetrating the walls.* So vast are the collections in the *perivenous spaces* that the whole cavity is occasionally filled, and backward pressure from the plugs and compression of the vessel from the outside have attained such a height that in a number of instances the vessel's walls have ruptured and *red corpuscles* are intermingled with the white and fill the space completely." These features are well illustrated in the annexed photographs. The center of Fig. 8 shows "polynuclear leucocytes in the perivascular space of a small intermediary vessel compressing its walls," while Fig. 9 shows "leucocytes in the blood in a cross-section of a large vein." The fact that the leucocytes are found in the "perivenous spaces" and "within the lumen of the vessel," coupled with the observation that they are "seen *penetrating* the walls," so clearly point to the process involved that the following conclusion imposes itself: *The blood* (we have seen that even *red* corpuscles are present) *of the axon evidently finds its way into a lymph-space connected with a vein, thence to the general circulation.*

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[54] Gray: *Loc. cit.*

Still, there is a feature of the whole process which requires elucidation. Why should the *veins,* which, of course, communicate with channels through which the blood can be freely evacuated, become *engorged* under the influence of the adrenal stimulation induced by alcohol? Engorgement of the arteries, their capillaries, the neuroglia channels, and the dendrites is a normal consequence of adrenal stimulation; but, the veins being outlets, such is not the case with the venous engorgement. This anomaly is accounted for by the now generally admitted fact that the vessels of the cerebral substance *per se*

Fig. 8

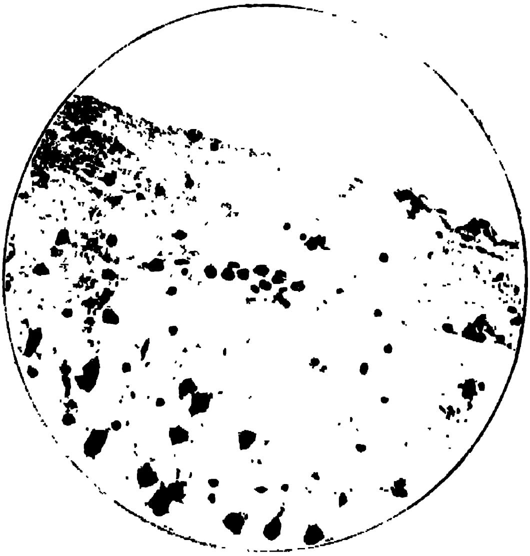
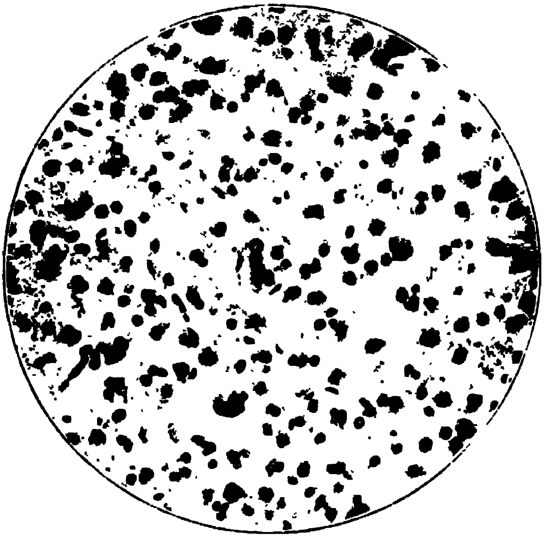


Fig. 9



LEUCOCYTES IN THE PERIVASCULAR SPACES AND IN VESSELS, AS A RESULT OF ACUTE ALCOHOLIC POISONING. *[Berkley.]*

[*Johns Hopkins Hospital Reports.*]

are not supplied with vasomotor nerves. "Vascular nerves may be found without trouble or difficulty in muscles, glands, etc., by the silver and other stains," writes Berkley, "but in the substance of the encephalon they are never to be seen with similar staining methods; hence it is fairly reasonable to suppose that they are not present in this location and that some other controlling mechanism takes their place. I have most carefully looked for them in many brains, both human and of the lower animals, but have never seen the slightest trace of their presence within the nervous structures. . . . Tuke and Andriezen, who made researches in the same field, have also failed to find them." As I will have occasion to show, this is an extremely important factor in the pathology of all toxæmias, mental and nervous diseases, for it indicates that *any marked rise of blood-pressure due to toxics, drugs, etc., causes vascular engorgement of the vascular channels of the brain-substance simultaneously with the engorgement of the peripheral capillaries of the other parts of the organism.*

Under these conditions contraction of the central vascular trunks through excessive adrenal activity causes not only congestion of the surface, but also of the brain. Strikingly confirmatory of this fact are the following statements of Professor Foster's: "It is argued that, in the absence of vasomotor nerves of their own, the cerebral vessels are wholly, so to speak, in the hands of the general motor system; so that when the blood-pressure is high, owing to a large vasoconstriction in the abdominal viscera, more blood must necessarily pass to the brain, and when, again, the pressure falls, through the opening of the splanchnic flood-gates, less blood necessarily flows along the cerebral vessels." . . . "Again it has been observed that certain drugs have an effect on the volume of the brain quite incommensurate with their effect on the vasomotor system."

If this testimony is sound and the interpretation of the data available is exact,—my conception of the neuron's inherent functions coincides with some of the main conclusions reached by Deiters, Gerlach, Golgi, Forel, and Cajal. In outlining their conclusions, however, I will only refer to those which are directly connected with my views, as a general review would take up too much space.

Deiters (1855) affirmed the prevailing theory—undemonstrated at the time—that the nerve-cell was supplied with two kinds of processes, the protoplasmic and the nervous, the latter constituting the nerve-fiber. Gerlach confirmed the views of Deiters, and showed that the protoplasmic processes subdivided into a fine reticulum, which, he thought, anastomosed with that of other cells. Golgi then demonstrated that, besides the two kinds of processes described by Deiters, there were given off collateral processes which, with the nerve-process, or axis-cylinder, constituted the only truly nervous structures of the cell, the other processes and the cell-body being purely nutritional. The subdivisions of the protoplasmic processes or anastomoses were not, in his opinion, continuations of those of other nerve-cells, either by continuity or through nervous networks, though some of the protoplasmic extensions were connected with neuroglia-fibers and blood-vessels. Forel contended that the entire cell and its processes were simultaneously functional and nutritional. Ramón y Cajal concluded that net-works of nervous fibrils did not unite the collateral processes, and, these being absolutely free, there could be no continuity of nervous substance between them, contiguity of their extremities alone prevailing.

I need hardly emphasize the fact that Golgi's views are strikingly confirmed by my own; indeed, had this great histologist converted the neuroglia-fibrils connected with blood-vessels into blood-channels, our interpretations would have been similar, though reached from entirely different directions. And I must admit that I consider this striking similarity, apart from the single line of research to which I have devoted all these pages,—*i.e.*, the histological chemistry of the circulation of the nervous system and the manner in which nervous energy is produced,—as a strong indorsement of my own conceptions. While Forel is fully sustained by my analysis when he asserts that all the parts of the neuron are simultaneously functional and nutritional, Golgi is likewise fully sustained when he considers the collaterals and the axon as the truly nervous structures, the others being nutritional. We have seen that the dendrites connected with the neuroglia-fibrils are really blood-channels. True, they are covered with gemmules and lined with myelin, a feature which shows that they serve for the formation of nervous energy; yet this energy is not utilized in these dendrites, but by the collaterals, in addition to that elaborated by their own myelin. Nor is the greater part of the blood which courses through the main dendrites used by them; it passes into the cell-body: a great center for the *production*, we have seen, of nervous energy, which energy is mainly utilized, not by the cell-body *per se*, but by the dendrites and the axon through which the whole neuron's blood is continuously passing.

Golgi's observation that some of the protoplasmic processes were connected with neuroglia-fibers and blood-vessels furnishes histological proof that my interpretation of the manner in which the neuron is connected with the circulation is based on solid premises. The prevailing ideas, however, as to the nature of *neuroglia* normally suggested that his views included a nervous net-work as intermediary between cells, neuroglia-cells being likewise considered as truly nervous structures. Hence the affirmation of Cajal that collaterals were totally independent of one another, especially if he gave neuroglia-fibers and cells the credit of only being what they are now generally thought to be: *i.e.*, a "peculiar ground-substance," in which the "blood-vessels, the nerve-cells, and nerve-fibers" are "imbedded." The neuron *is* autonomous functionally: *i.e.*, as a nervous organ, ***each neuron is connected with the circulation by its own neuroglia blood-channels.*** An illustration of the continuity of neuroglia-fibers with the cerebral circulation is afforded by Berkley's experiments with alcohol. "Besides the swellings in the course of the dendrons," says this author, "we must always be on the watch to exclude certain processes of the support neuroglia-cells that traverse long distances of the cortex and exhibit a *pearl-string* swelling in the course of the fiber."

Are nerve-cells contiguous, as thought by Cajal? Berkley states that the great Spanish investigator writes "that the ascending fibers of the cortex, which have a vertical or oblique course through the medullary layers, have their points of contact with the protoplasm of the dendritic structures in the *intervals* between the short transverse processes (gemmulæ) around which the ascending fibers twine." In other words, the tips, or extremities, of the axon of one neuron, instead of being in contact with the tip of the gemmule, touch the intervals between gemmules. "Such a discharge of the nerve-forces from cell to cell taking place at hundreds of indefinite points," continues Berkley, "could not fail to produce stimuli that would be more often aberrant than direct, and, in all likelihood, such an arrangement would produce the utmost confusion of thought and motion, a veritable inco-ordination of the cerebral functions, which would reduce direct cerebration to a nullity." This point seems to me to be well taken, and the identical argument prevails as regards contiguity, for if, as I believe, myelin and the oxidizing substance are constantly in contact in the neuron,—*i.e.*, the cell-body, dendrites, and axon,—nervous energy is continuously being formed, and promiscuous contact with the dendrites of other cells would give rise to the untoward effects enumerated. In the light of my views, therefore, continuous contiguity between neurons through their dendrites or axons does not appear possible.

How do neurons transfer their nervous energy to other neurons? Berkley states that it is "more than probable that it is only at the free bulbous terminations of the nerve-filaments [axons] that we have naked protoplasm, and from this uncovered nervous substance the dynamic forces, generated in the corpora of the nerve-cells, are discharged, through contiguity, on to the protoplasmic substance of other cells. Thus, in contradistinction to the hypothesis of Cajal," continues the author, "we have only comparatively few points at which the nervous forces may discharge themselves from axons to the protoplasm of other cells, and these are seated at definite points on the terminal arborizations of the nerve-filaments, for otherwise what would be the necessity of a terminal apparatus were the nerve-conductors free to discharge their dynamic forces at any point at which they came in contact with the substance of a dendron?"

It seems to me that the feature to ascertain in this connection is the character of the functions of the gemmules. Why do these little projections of the dendritic walls become erect during the cerebral congestion induced by poisons? Are they really intended to receive discharges of nervous energy from the bulbous tips of axons? They outnumber the axonal end-organs out of all proportion. Indeed, their multiplicity around all the stems excepting the axon hardly points to them as terminals endowed with such important functions as those attributed to them. Again, Berkley states that "the twigs of the dendrites and the fibers touch each other frequently and in a manner that appears to be perfectly indifferent for the different kinds of nervous substance, receptive and projective." Such promiscuousness plainly testifies, it seems to me, against the identity of the substances in contact being exposed surfaces capable of transmitting to each other a stream of nervous impulses.

In the light of my views, however, a function perfectly in keeping with the experiments of Goddard in puppies, of Demoor with morphine, of Berkley with alcohol, ricin, serum, etc., suggests itself. We have seen that during functional activity the gemmules project, while during inactivity they recede. If we now connect these facts with the presence in the gemmules of a thin layer of myelin immediately under their external or limiting covering, and concede that the latter and the myelin take part in the formation of each gemmule, it will become evident that during the erethic state the surface of myelin exposed to the action of the oxidizing substance of the plasma will be greatly increased and the proportion of nervous energy produced correspondingly augmented. Retraction of the gemmules, on the other hand, by emptying them of their plasma, will normally cause diminution of energy-production, the myelin of the main channel sufficing to sustain nutritional functions during sleep, for instance, when the gemmules are retracted. We have what seems to me a counterpart of these minute structures in the muscle-cell, the myosinogen of the latter being replaced by the myelin. We have also, in the processes outlined, an *active* and a *passive* functional stage in keeping with other organs. All this so thoroughly coincides with the various attributes which the gemmules have been shown by various investigators to possess, that I feel warranted in concluding that *the gemmules are peripheral extensions of the dendritic walls having for their purpose to increase, when erect, the area of* *myelin exposed to the action of the oxidising substance of the plasma, and thus to render the dendrite functionally active:* i.e., *able to transmit or receive nervous impulses. When the gemmules are retracted or collapsed, therefore, functional activity is in abeyance, as during sleep, anæsthesia, etc.:* i.e., *they are unable to transmit or receive impulses.*

This tends to show that none of the gemmules serve *per se* to transmit impulses, and that the dendritic tips must alone be endowed with this function. That such is the case seems to me suggested by Fig. 2 on the plate opposite page 550, which exemplifies the condition of a dendron before the engorgement induced by ricin has become far advanced: *i.e.,* at a time when the dendron's lumen has not as yet become completely blocked. The two central dendrites may be seen to terminate with bulbous tips, while the remaining gemmules immediately adjoining the latter are not apparently enlarged. This would point to the enlarged extremity as a dissimilar structure in respect to the gemmules, a terminal organ as it were. Again, the gemmules and terminal organ would have presented a certain degree of resemblance under the influence of the engorgement under the action of poisons, had they been similar; their appearance, on the contrary, suggests dissimilarity. Berkley states that, "so far as the end-apparatus of the collaterals from the psychical cells is concerned, the terminations of the intermediary cells, the fibers entering from the medullated masses, all have the same end-apparatus, which consists solely of a simple freely terminating *bulbous ending,* situated upon the *extremity* of the finest branches of the nerve-fibers." As he then refers to figures in one of his illustrations which represent axons supplied with bulbar extremities, I infer that it is to the dendritic terminals that he alludes, and not to those of the gemmules, as a broad application of his preceding paragraphs might suggest. If the bulbous terminals of the entire dendrite as well as the axon are referred to, the quoted lines afford additional evidence tending to show that the dendritic extremities alone transmit or receive impulses. Indeed, in the article in which chronic alcoholic poisoning is studied, Berkley remarks: "The process of tumefaction *always* appears to begin at or near the fine extremity of the dendron, be it the extremity of the main apical process or one of its *collateral* branches, and not infrequently the *extreme termination* of the dendron, is seen to be somewhat swollen *when no other portion of the cell is involved.*"[56] He also states that "in his description of the mode of ending of the *collaterals* of the great pyramidal cells" Cajal "describes their finest branches as terminating freely by a *nodosity.*" All these facts seem to me to warrant the conclusion that *each of the collateral dendrites of a neuron and each axon, or subdivision of the latter, is supplied with a bulbous end-organ.*

How is an axonal end-organ of one neuron functionally related to that of a dendrite of another neuron? Berkley, alluding to the subdivisions of the axon, each of which is supplied with its bulbous end-organ, says: "These spherical apparatuses are closely adjusted against the bulbous tips of the gemmules, at times the approximation being so close that the impression is given of actual contact, though it should be remembered that the slightest overlapping will produce the same effect; and, on the whole, it is more probable that there is no actual contact, but that the *axonal discharges* of the stimuli overleap the infinitesimal distance between bulb and gemmule." For the reasons adduced, I do not think that the gemmules serve for the reception of impulses. These reasons also suggest that each axonal end-organ can only discharge its stream of impulses into the bulbous *terminal* of a neighboring dendrite, which bulbous terminal would, under these circumstances, present some analogy with the end-bulb of Krause, and, indeed, with several peripheral sensory organs. I have also submitted reasons that seem to me to offset the assertion that the end-organs actually touch. Indeed, that an "infinitesimal distance" between the efferent axonal end-organ and the efferent dendritic end-organ exists seems to be the only conclusion warranted by the histological picture, as described by Berkley. It seems to me, in other words, that *each of the bulbous end-organs of an axon, though apparently in contact with the end-organ of one of the dendrites of a neighboring neuron, may be separated from it by an infinitesimal distance.*

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[56] All italics are my own.

The bearing of this arrangement, as an element of function, asserts itself when the stress we have laid upon the *vibratory* character of a nervous impulse is recalled. When studying the nature of the functional activity of muscles, I had occasion to say, referring to the governing action of motor nerves: "As the vibratory rhythm of the impulse and that of the muscle always correspond, any variation of rhythm by the brain-center correspondingly modifies the muscular contraction." If we now analyze what this vibratory rhythm means when the dendritic end-bulb and the axonal end-bulb are separated by an infinitesimal distance, but one answer appears to suggest itself: *i.e.*, that there can be no flow of impulses from one to the other. But we must not lose sight of the fact that the contradictory histological pictures described by Cajal and Berkley are those of *non-living* cellular elements, and that death may leave the two end-bulbs juxtaposed, as seen by Cajal, or separated by an "infinitesimal distance," as seen by Berkley. Thus, each histologist is right in his way as regards dead tissue. But what of living structures? Cajal and Berkley will again assist us in reaching a deduction in this connection, for *each* investigator furnishes one-half of the main physical *function* involved: *i.e., vibration, which means rapidly alternating juxtaposition and separation of the bulbous end-organs.*

The rapidity with which the gap between the two terminals is opened and closed—*i.e.*, the *rhythm*—regulates, we have seen, functional activity. But can we conclude from this that non-activity of an organ means cessation of vibration of the bulbous end-organs involved in the function? We have seen that the nutritional processes of all tissues are continuous, nervous energy being supplied to the cellular elements as long as life lasts. Forel, as stated, was led by his admirable investigations to the conclusion that "living muscle appears to be so organized that without nervous stimulation it can live as little as the tropical animal can without warmth or the rose without water." This applies to all living tissues: a feature of the problem which necessarily implicates the continuous *development* of nervous energy and, as a consequence, an unceasing vibration of the end-organs. It seems to me, therefore, that, *inasmuch as the nutritional processes of the organism require a continuous* *supply of nervous energy, all the systemic axonal and dendritic end-organs are in a state of constant vibration.*

Analyzing muscular contractility, I stated that: "The impulse-wave [and the blood supplied the cell] simply sets the muscle-elements to a given vibratory rhythm, and they retain this whatever be the intensity of the exertion required. . . . This may aptly be compared to the manner in which a note on a violin is made loud or soft. The power with which the string is pressed upon with the moving bow modifies the intensity of the sound; but the note remains the same. This means that its pitch does not vary, and if, for example, the lower C is given, we will know that the sound-wave of that note represents two hundred and sixty-one vibrations per second. So may the *impulse-wave* transmitted by the brain through a 'motor' nerve be represented by a fixed number of vibrations. Retraction, the muscle being then most tense, is therefore characterized by the greatest number of vibrations." If this interpretation is sound, it is likewise applicable to the "to-and-fro" motions of the bulbous terminals which constitute vibration, the number of these motions within a given time representing a given intensity. Any modification of the number of these to-and-fro motions within a given time, therefore, correspondingly modifies the intensity of the resulting vibratory impulse-wave, *the* PASSIVE *state of function (that during which cell-nutrition alone occurs) being represented by the lowest number of vibrations, the* ACTIVE *stage (during which the function is in full sway) by the highest number of vibrations compatible with normal health.*

Still, in accordance with my views, this applies to the impulses transmitted by the posterior pituitary body, since this organ, directly and through its extension in the cord, governs the passive stage of function and incites the cellular elements, both through the terminal vasomotors and the net-works distributed to the cells themselves, to higher activity when the active stage becomes necessary. Can we say the same of the independent hemispheres? This carries us back to the circulation of the brain, for the question involves another: *i.e.*, whether the cerebro-spinal functions, active and passive, are carried out in a manner similar to that of all other organs.

I am now able to state that they are, for *the neuroglia-fibrils of the substance of the brain and cord represent their blood-supply, just as the cellular capillary net-work of any other organ represents its blood-supply.*

Indeed, we must not overlook the fact that, while the neuroglia-fibrils representing the capillary supply of the cerebro-spinal substance are not supplied with vasomotor nerves, the peripheral vessels connected with the organ are, thus furnishing it with what might be described as an *extrinsic* supply. This extrinsic system would thus be represented by the pial vessels, which, as shown by Andriezen,[56] are supplied with vasomotor nerves. "We find," writes this investigator, "that it is possible to stain the vasomotor nerves with Golgi's method. Starting from the carotid and vertebral plexuses we can trace them no farther than the circle of Willis by anatomical dissection (using a lens). Do nerves accompany the cerebral arteries as they go off from the circle of Willis; and, if so, how far; and what is their ultimate distribution? Our observations on the kitten's brain show that bundles of nerve-fibers accompany the middle cerebral artery (the one specially chosen for our study) and its branches in the pia. These fibers run in tortuous and zigzag fashion, and in the finer pial branches they can be seen to form a very fine (non-anastomotic) plexus of fibrils lying between the outer and the muscular coats. From this *perimuscular* plexus terminal fibrils issue which, running a short distance along the muscular layer either longitudinally, transversely, or obliquely, end in small spherules: little ovoid bulb-like arrangements abutting against the muscular elements (cells). We have succeeded in tracing these terminals and their distribution to the finest pial cells, but no farther. The intracortical continuations of the pial vessels have constantly failed to give us the least evidence of this perimuscular plexus, which therefore—so far as our investigations go—we are compelled at present to imagine as *stopping with the pial branches,* and *not* continued along the intracortical vascular branches."[57] This evidence, added to the facts already outlined concerning the pericerebral vascular supply, seems to me plainly to indicate that *the cerebral circulation is governed, as is that of the arterioles of the body at large* (by the posterior pituitary body, as we shall see, pages 982 and 1259), *through the vasoconstrictor nerves of the pial vessels, which are terminals of the sympathetic system.*

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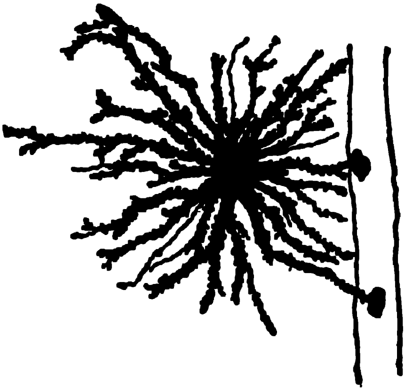
[56] Andriezen: Brain, Winter, 1894.

[57] The word "not" is alone italicized by Dr. Andriezen.

This only furnishes us, however, the functional mechanism of the *passive* stage. In other words, the nervous energy developed owing to the presence of a given proportion of adrenoxidase (brought into contact with the myelin through the tonic vascular contraction insured by the general motor system) only causes the entire brain to create the nervous energy which, as we have seen, is essential to its own life. But how is the *active* stage incited in any one part of the cerebrum?

As is well known, groups of individual muscles may be caused to contract simultaneously, while some of the muscles which enter into the formation of these groups may be replaced by others. This is well exemplified by the mechanism of piano-playing: the index, thumb, and little finger, to form one chord; the annular and thumb to form the next, etc. Tracing this mechanism back to the structure which *incites* and *governs* the muscular adduction and abduction through which the keys are struck and released, we are brought back to a neuron. But how is the *neuron* incited to activity? In other words, how is the increased speed of blood through its myelin-lined dendrites, cell-body, and axon incited and governed? Can we ascribe this all-important function to the posterior pituitary body? We have seen that removal of the hemispheres did not prevent muscular action; a frog can swim, a pigeon fly, etc., and, indeed, continue to live a considerable time—months—if carefully fed, notwithstanding the absence of its hemispheres. This suggests that, while the posterior pituitary body either directly or indirectly incites and governs the functional activity of all organs, exception should be made of *the brain,* though it governs the circulation of this organ.

Still, the cellular elements of all organs are supplied with a net-work of terminal *nerves,* and it is through the intermediary in this net-work that its functional metabolism is governed by the posterior pituitary. How is the same function fulfilled in the hemispheres: *i.e.,* how are its cells, the neurons, "incited and governed?" Are they also supplied with a net-work of fibrils which receives impulses from the posterior pituitary body? There is no evidence available to suggest that such is the case, and the functional relationship with the latter through the vasomotor supply of the pial vessels is the only link between the two organs that existing data permit us to accept. If, therefore, a regulative mechanism exists, it must be one connected with the vascular system, and so disposed as to enable it to govern the circulation through one or more neurons simultaneously. It must supply its own nervous energy, for we have seen that Andriezen found the vasomotor nerves to distinctly terminate upon the muscular coats of the pial vessels; indeed, it must be as autonomous an organ as is the neuron itself.



"A PROTOPLASMIC NEUROGLIA-CELL FROM THE HUMAN BRAIN (FOURTH LAYER OF CORTEX) SHOWING TWO EXPANDED CONICAL DISK-LIKE ATTACHMENTS TO A VESSEL." (*Andriesen.*)

Such an organ we have, it seems to me, in the neuroglia-cell shown in the above illustration, which Andriezen has named the "protoplasmic neuroglia-cell," and describes as follows[58]: "The protoplasmic glia-cell has a distinct cell-body, which is irregularly oval, frequently pyriform. Its various protoplasmic processes are of moderate length; they exhibit *great variations of caliber,* some being stout and coarse and others exceedingly fine. These processes are also *dendritic:* a thing never seen in the stellate cells. A most striking feature is the shaggy granular contour, as if a fine moss constituted the protoplasmic processes. . . . Further, by one or more of their *coarser* processes the protoplasmic cells are attached to the perivascular sheaths. The figure [on the opposite page] shows the cell with two such vascular processes, each *attached to the vessel* by a conical disk-like expansion ('foot')."

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[58] Andriesen: British Medical Journal, July 29, 1893.

These characteristics of this cell speak clearly in favor of my view that neuroglia-cells and fibrils are channels for blood. Bearing directly upon the question in point, however, is the fact that this cell, as indicated by its gemmules and its dendritic appearance, must be supplied with myelin. The association of this myelin with the blood-plasma in transit at this point—*i.e.,* so close to the blood-vessel—seems suggestive, for, if the illustration is closely examined, dendrites are not alone found around the cell, but also fibrils, which start from various parts of these dendrites. That these protoplasmic neuroglia-cells are directly connected with the blood-vessels so as to admit plasma is demonstrated by the fact that they also take part in the engorgement of neuroglia structures that follow poisoning. "The bodies of the *mossy* neuroglia-cells," writes Berkley, alluding to the effects of ricin poisoning, "are larger than normal, rounded, sometimes globular in outline, and the tentacles are thickened and knotty. There are general evidences that these structures of the *lymphatic* system are undergoing modifications of a pathological nature." I have already stated that this "lymph" was, according to my view, its next o' kin: *i.e., blood-plasma.*

Referring to the paper from which I have just quoted, Andriezen remarks[59]: "We also stated at the time that the evidence of staining with Golgi's method shows us a system of lymph-spaces surrounding the cell-body and its branches. Careful and fresh observation confirm us in this opinion, viz.: that there is *an exceedingly fine system of canaliculi and lymph-spaces* surrounding the body, and dendritic processes of the protoplasmic glia-cell, and directly continuous with the perivascular lymph-spaces." If the annexed sketches *by Andriezen* are now examined and *interpreted from my standpoint,* additional testimony in favor of my conception of the whole mechanism of brain-function will appear. Indeed, the *canaliculi* are evidently the openings into the neuroglia-fibrils. But these microscopical channels, which are often one-sixth the size of a blood-corpuscle, would soon be blocked were the latter allowed to reach them. There is interposed between them, therefore, a lymphatic membrane, similar to the one which, as we have seen, forms the lymph-space from which veins start. Here, however, a double purpose is served, as shown in the sketch. It forms two cavities: the one surrounds the blood-vessel, and

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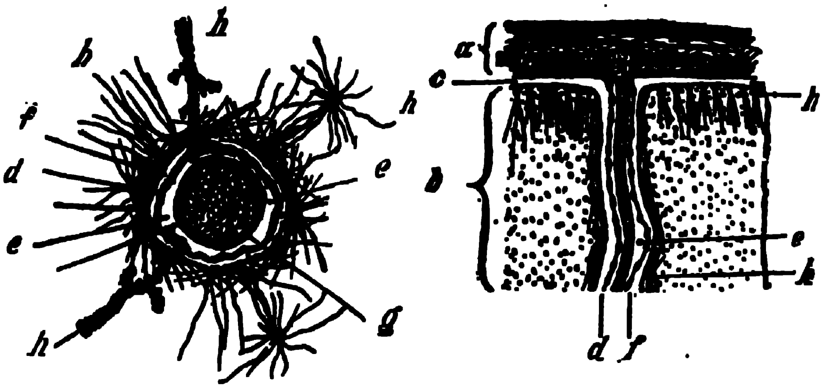
[59] Andriezen: Brain, Winter, 1894.

Fig. 1. Fig. 2.



RELATIONSHIP OF THE VASCULAR AND LYMPH CHANNELS IN THE BRAIN. (*Andriesen.*)

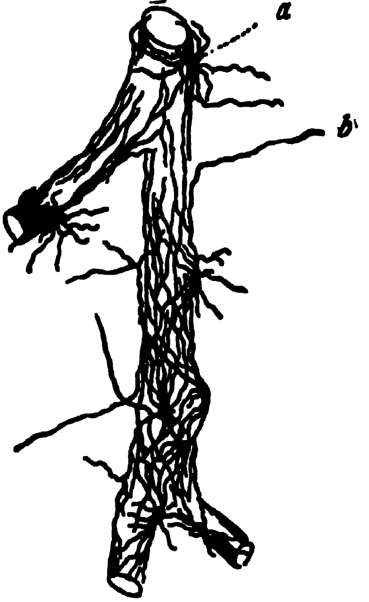
a, Pia-arachnoid. *b*, Brain-substance. *c*, Epicerebral space. *d*, Adventitial sheath. *e*, Intra-adventitial space. *f*, Extra-adventitial space.

(According to my view, these are all blood-channels: The blood arrives in pial artery (g), and escapes through the walls of the latter into the "intra-adventitial" space (e). Part of the plasma of this blood passes through sheath d into the "extra-adventitial" space (f) and enters neuroglia-fibers and cells (h, h, h), and then passes into the apical dendrites of neurons; the rest of the plasma and all corpuscles return to the veins by way of the "intra-adventitial" space at e.—S.)

represents the channel connected with the venous system, to which all corpuscles return; the other, or external, space receives only the blood-plasma which has passed through the membrane. The latter, being mainly composed of endothelial plates, is therefore phagocytic and bactericidal, and thus admits into the neuroglia canaliculi not only plasma relieved of all its cellular elements, but also asepticized adrenoxidase-laden plasma. The outside of a vessel covered with a neuroglia-ridden sheath is shown in Fig. 3.

The two kinds of neuroglia-cells may be seen to take part in the formation of the external net-work of fibrils in the illustration on page 586. It is here, it seems to me, that the governing attribute of the "protoplasmic neuroglia-cell" shows itself, as suggested by the dendritic appearance of its extensions. Indeed, Ranvier has been led to conclude that the other variety of neuroglia (stellate) cell is not much more than a mass of aggregated fibrils in transit, the latter passing through them without forming part of the cellular structure. Still, as it contains a nucleus, it may possess a regulative action. The larger cell, however, imposes itself as an organ of a very active kind—capable probably of playing in the brain the part that the vagus plays in various organs: *i.e.*, to incite

Fig. 3

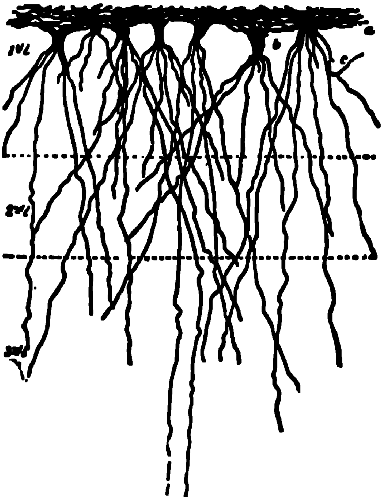


BLOOD-VESSEL OF THE HUMAN BRAIN, SHOWING SEVERAL NEUROGLIA FIBER-CELLS SURROUNDING IT AND FORMING A FELT-WORK (PERIVASCULAR SYSTEM). (*Andriezen.*)

a, An encircling cell. *b*, Perpendicular neuroglia-fiber entering the sheath at right angles from a distant (extrinsic) cell.

active function and govern it in the neurons with which it is connected, either directly or through the intermediary of other neurons. The connection with the latter would not be established by continuous fibers, but through their end-bulbs, the axonal of the one to the dendritic of the other, etc., in order to allow of the transmission of *vibratory* impulses. Referring to these larger "protoplasmic" ganglia cells, Andriezen writes: "They occur abundantly throughout the gray matter, in all the layers of the cortex, but are rare in the white substance." Indeed, according to my views, the latter is a mass of axis-cylinders coming from the upper strata, and surrounded by their myelin, wherein energy increases with distance: a true "avalanche"—using Pflüger's expression—of nervous force toward the lower cerebral structures.

The predominating function of both varieties of neuroglia-cell asserts itself, however, when the characteristics of the cortical layers are reviewed. The first, or molecular, layer contains but few nerve-cells, according to Andriezen. Its proximity to the pial vessels normally suggests that, if glia-cells are intermediaries between these vessels and the brain-substance's circulation, they should occur in large quantities in this region. "Its outermost, or superficial, region is formed of a system of neuroglia fiber-cells," says Andriezen, and by means of the annexed illustration, among others, he emphasizes the varied directions and the length their extensions may assume. But if the illustration on page 586 is examined, the manner in which these cells (according to my interpretation) are supplied with plasma may be easily understood. As shown therein, the pial vessel dips into the brain-substance, surrounded by its lymphatic membrane in such a manner, we have seen, as to form two spaces, the internal of which is for the blood and corpuscles to be returned by the veins to the general circulation; the other, or external space, being that in which the plasma for the neuroglia-cells passes after penetrating the lymphatic membrane, in order to reach the neuroglia-fibrils. This affords a supply to both kinds of cells, which are seen to line the plasma-containing space. That both are intimately connected with the circulation appears to me beyond doubt; that the mossy, or protoplasmic, cell is endowed with some function other than as a mere distributing center is as likely; that this function should be to regulate the circulation in the neurons, or groups of neurons with which it is connected (as shown by the effects of poisons upon all structures thus connected), is strongly suggested by the fact that, while the need of such a regulative system is evident, there is no discernible or known organ or system of organs, directly connected with the pial blood-vessels, other than these cells to which this important function could be ascribed. The following conclusions, therefore, seem to me warranted:—

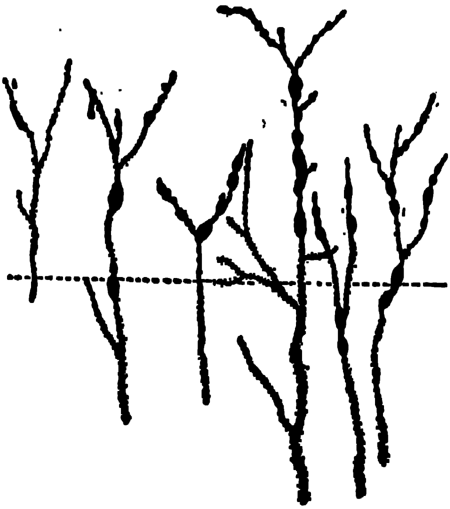


SEVEN CAUDATE NEUROGLIA FIBER-CELLS FROM THE HUMAN BRAIN-CORTEX (FIRST LAYER). (*Andriezen.*)

a, Tangential fiber-system. *b*, Cell-bodies. *c*, Descending fiber-system. The dotted line shows the limit between the first and second and the second and third layers.

The neuroglia-cells are the intermediaries between the general circulation and the capillary system (neuroglia-fibrils) of the brain-substance. The smooth stellate cell seems only to serve for the equable distribution of the blood-plasma to the neurons, while the mossy, or protoplasmic, cell presents the attributes of an organ to which the function of inciting a group of neurons to action by activating its blood-supply and of governing the quantity of nervous energy produced in these neurons can be ascribed.

Judging from the admirable histological work of Andriezen and Berkley, the engorgement caused by poisons affects the three upper layers of the cortex most markedly. The bead-like swellings of the first-layer dendrites are well shown in the annexed illustration, the lesions being those found in alcoholic insanity. The second layer and third layer are represented by the plate opposite page 550, reproduced from Berkley's article, ricin poisoning, as previously stated, having been the cause of the cerebral engorgement. The cells of the last, or fourth (polymorphous), layer are not shown, but the fact that



TERMINAL TUFTS AND ENDINGS OF THE PROTOPLASMIC APICAL PROCESSES IN THE FIRST LAYER (HUMAN BRAIN-CORTEX).
(*Andriesen.*)

Showing bead-like and moniliform swellings, coalescence of fine miliary granules in place, and loss of fine granulation in the most affected parts. The dotted line marks the limit between the first and second layers. Alcoholic insanity.

Marchi found that the ependymal neuroglia-cells sent a central extension to the optic thalamus, where it divided and became attached to the blood-vessels, shows that the circulatory mechanism I have described applies to the entire cerebro-spinal system. Briefly, *the cerebro-spinal system is built up of neurons supplied with adrenoxidase-laden blood-plasma through the intermediary of protoplasmic neuroglia-cells, which regulate the volume of this fluid admitted into the neurons and, thereby, their functional activity.*

THE POSTERIOR PITUITARY BODY AS THE SOMATIC CENTER OF THE NERVOUS SYSTEM.

Howell,[60] in the course of experiments which led him to conclude that "the infundibular lobe of the hypophysis (the posterior pituitary) is, in all probability, not a rudimentary organ, but a structure that has some important physiological activity," found, as I have already stated, that "the extracts of the glandular lobe (the anterior pituitary) have little or no perceptible effect when injected alone. Extracts of the small infundibular lobe, on the contrary, have a distinct and remarkable effect upon the heart-rate and blood-pressure, an effect which resembles, in some respects, and differs, in others, from that shown by suprarenal extracts."

We have seen in our previous analysis of these observations that the symptoms produced were those of suprarenal overactivity, and that the extract acted as did adrenal extract; the heart-beat was "not only slowed, but considerably augmented in force," says Howell, "as shown by tracings taken with a Hürthle manometer," etc. When both vagi were cut or a little atropine was given, the slowing of the heart was less marked. The result of vagal section is evident. As to the atropine, it prevented the slowing because, when added to the pituitary extract, it modifies its action, by inhibiting the functions of the adrenals as it does those of other glands. But an interesting query imposes itself in this connection: The extract having at first stimulated the activity of the adrenals, how did the latter, through the increased oxidizing substance, bring about increased vagal action? The answer is easily reached: the posterior pituitary being also increasingly supplied with oxidizing substance, its activity is likewise increased. This emphasizes an important feature: *i.e.*, that *the posterior pituitary is* functionally stimulated, as is any other organ, by the oxidizing substance in the blood passing through it. Indeed, the nerve-fibers which Berkley found to accompany the arteries suggest the presence of a functional arrangement similar to that of any organ, while the presence of so many neuroglia-cells at the apex—*i.e.*, where the posterior pituitary meets the infundibulum—indicates that the neurons which they supply are the seat of marked functional activity.

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[60] Howell: "Transactions of Congress of American Physicians and Surgeons," vol. iv, p. 83, 1897.

The feature brought out by Howell's experiments, however, is that the posterior lobe (including the *pars intermedia* as recently shown by Herring[60a]) contains an active agency. This harmonizes with my views, since, as we have seen, the anterior lobe is, to a certain degree, passive in that it is stimulated to an inordinate degree only when toxics are present in the blood, while its normal activity is sustained by the secretion of the thyroid gland. Though the purpose of both organs is similar, therefore,—the conversion of chemical energy into nervous energy,—the manner in which this is done is not similar. Indeed, in the posterior lobe, the exciting agency is, as just stated, precisely as it is in any organ: *i.e.*, oxygen. The posterior pituitary must, therefore, become physiologically active through the same chemico-physical process that prevails elsewhere in the body.

Indeed, we have seen that the posterior lobe is, in reality, but an aggregate of neurons—and a precious aggregate it must be, ensconced, as it is, in a bony cradle and resting on a pillow of blood, to preserve it against shocks or traumatisms! That, like all neurons, this aggregate depends mainly upon a phosphorus-containing ground-substance has been shown. I will recall that Cyon,[61] in the course of a large number of experiments (since confirmed by Masay, see pages 983 to 989), observed that: "1. Any, even slight, pressure upon the hypophysis (*i.e.*, both organs) immediately gives rise to a sudden variation of blood-pressure and to a notable reduction in the beats of the heart, the strength of which is at the same time considerably increased. 2. Electrical stimulation of the hypophysis, even with extremely weak currents, produces exactly the same phenomena as does mechanical pressure, but in a much more intense manner. 3. Extract of hypophysis, injected into the veins of an animal, produces upon the heart and upon blood-pressure effects that are analogous to those caused by electrical and mechanical stimulation of this organ." I have pointed out that this pituitary extract does not prove the existence of a secretion at all, and that its action was due to the presence in the organ—as in all sympathetic structures, of chromaffine, *i.e.*, of adrenal substance. Indeed, Oliver and Schäfer in 1895 found that pituitary extract could be boiled without destroying its action—a property which a ferment such as the adrenal principle possesses alone. This added to the chromaffine and adrenalin reactions and the fact that the effects of pituitary extract are precisely those of adrenal extract shows the fallaciousness of the secretion doctrine. Conversely the facts reviewed the presence of phosphorus, noted by Rossbach, and the effects of direct stimulation, plainly show that *the posterior pituitary, being mainly composed of neurons and their protoplasmic extensions, is the seat of reactions similar to those that prevail in other nerve centers.*

[60a] Herring: Quarterly Journ. of Exper. Physiol., vol. 1, p. 281, 1908.

[61] De Cyon: Archives de Physiologie, July, 1898.

The intrinsic processes upon which the physiological functions of neurons and nerves depend seem to me to be represented in the foregoing pages, but I have still to account for the "stormy processes in the nerve-fiber" to which Barker refers: *i.e.*, the exacerbations through which *passive* functions become *active.* Can we attribute these to the cells in the several centers? "Notwithstanding almost infinite minor variations in form," says Professor Barker, "the neurons in the most different parts of the nervous system present surprisingly similar general external morphological characteristics." We have seen, by the details furnished by the histological studies of Berkley, that such is not the case with the neurons in the posterior pituitary. Indeed, there are in this organ *ten* cells, exclusive of four of the neuroglia type that differ in morphological characteristics, each of which receives from Berkley a separate description. Not only do all the axons of the cells in this lobe point upward, but the diversity of cellular shapes is beautifully illustrated in the plate opposite page 594, a transverse vertical section of the infundibular region.

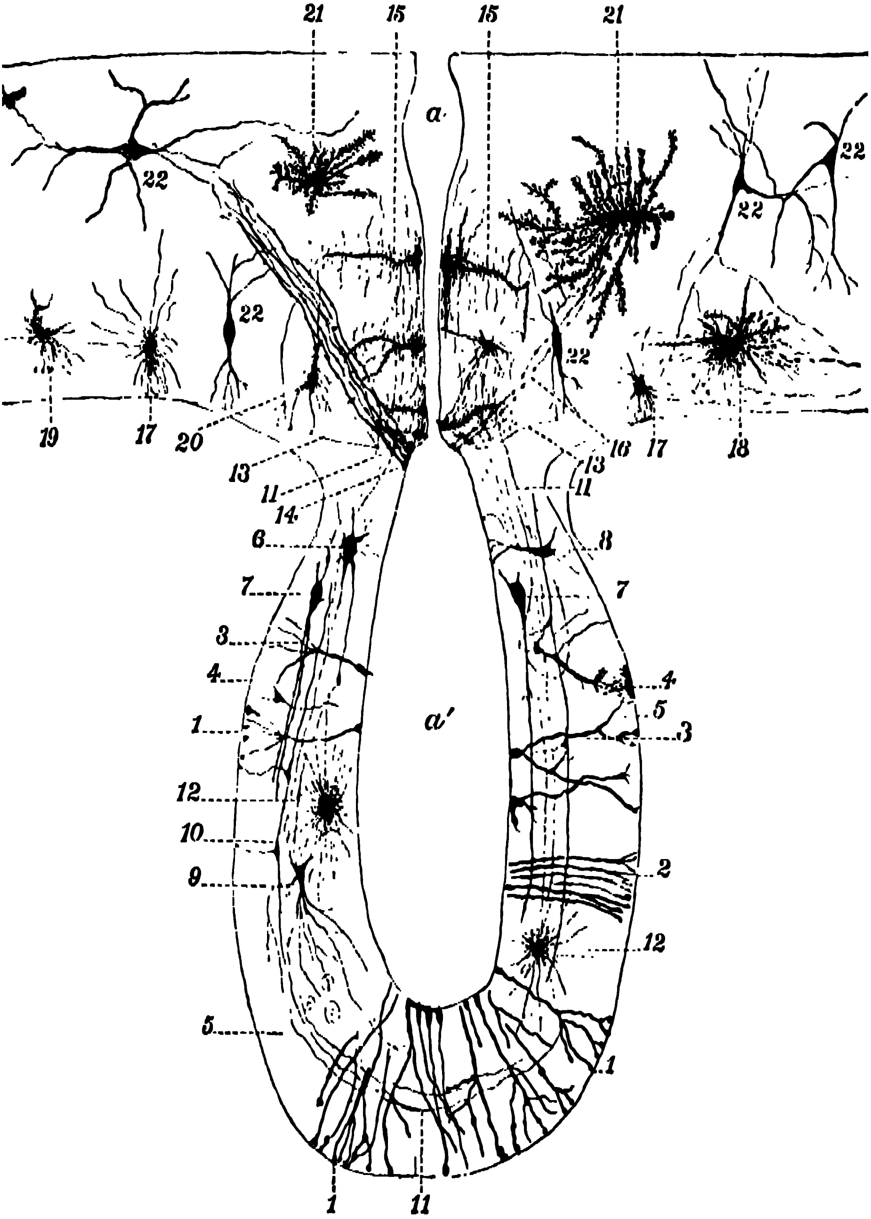
We have seen that above the infundibulum—*i.e.*, in the structures of the third ventricle—he found "varieties of ependymal neuroglia-cells, previously supposed to have entirely disappeared from the central nervous system," etc., and which were thought to be confined to "reptiles, amphibia, and fishes." The physiological rôle I have ascribed to neuroglia-cells and fibers further emphasizes the importance of these structures and of the marked nutritional activity of which they are the seat. As a complement of this I showed that Andriezen traced a direct nervous connection in all classes of vertebrates between the "posterior lobe of the pituitary," on the one hand, and "the olfactory center" and the "bulbo-spinal centers," on the other.

When these facts and others reviewed are placed side by side with the adduced evidence (1) that the middle brain is the seat of a nervous mechanism through which highly differentiated afferent impulses meet with response, and (2) that the structures to which Berkley and Andriezen refer are contained precisely in the central gray matter which Foster considers as "perhaps in point of origin the oldest part of the brain" and which "seems to serve chiefly as a bed for the development of the nuclei of the cranial nerves," it seems clear to me that the posterior pituitary body is *a general center in which active functions are incited and governed in response to afferent impulses.*

TRANSVERSE VERTICAL SECTION OF THE INFUNDIBULAR REGION.

a, Lumen of ventricle. *a'*, Lumen of infundibulum. 1, Primary forms of ependymal neuroglia, the processes extending from a cell-like body at the edge of the ventricular cavity to the subpial limit. 2, Coarser and less ramified variety of ependymal cell. 3, Coarser ependymal cells, branching within the inner half of the infundibular wall. 4, Portions of ependymal cells with tufted subpial branchings. 5, Unstained nerve-cells. 6, Pyramidal cells with long, fine processes. 8, Transversely lying cells of small size with knobbed extremities. 9, Pyramidal cells with large numbers of apical processes. 10, Probable axis-cylinder extension of pyramidal cells with thickenings, and rectangular extensions to the subpial limit. 11, Nerve-fibers passing from the infundibular wall into the tissues along the border of the ventricle. 12, Burr-like cells of the infundibular wall. 13, Line of the floor of the brain. 14, Long-rayed ependymal cells of the juncture of the ventricular and infundibular cavities. 15, 15, Fir-tree ependymal cells of various sizes and forms lining the border of the ventricle. A few of them are seen to have rounded knobs adjusted against the pial limit of the basis cerebri. 16, Neuroglia cell approximating the short-rayed type of Golgi. 17, 17, Sustentacular glia-cells of the inferior border of the tuber cinereum. 18, 19, Glia-cells with numerous long and stout hairy processes from the bodies, and thicker projections, probably transition forms between the sustentacular cells and cells of later development. 20, Probable nerve-cell resembling some of the glia-cells. 21, 21, Large mossy cells situated at some distance from the ventricular border. 22, 22, Nerve-cells of different forms. (*Berkley.*)

A neuron, we have seen, presents the attributes of other organs; that the analogy includes the functional limits of these



SEMIDIAGRAMMATIC TRANSVERSE VERTICAL SECTION OF THE INFUNDIBULAR REGION OF THE BRAIN. [Berkley.]

[*Brain.*]

organs is very probable. Under these circumstances and taking the digestive system as example, a group of neurons constituting the origin of a nerve would be able automatically to continue its *passive* functions between meals. But just as the onset of digestion, the active functional state of the stomach, involves an increase of the volume of blood supplied to its muscular and secretory elements, through vasodilator impulses, *so would a nerve-center, when required to assume the active phase of its functions receive more blood (adrenoxidase-laden plasma) through arterial vascular elements governed by the posterior pituitary.*

Professor Foster's reference to the central gray matter as a bed "for the development of the nuclei of the cranial nerves" suggests that the posterior pituitary might possibly supply energy for all cranial nerves. The complex origins and connections of the optic nerve would, under these conditions, convert the posterior pituitary into a source of energy, pure and simple, for general distribution. Ample evidence to this effect is submitted in the second volume.

This does not apply to the anterior lobe, however, although its *pars intermedia* governs the adrenals. Berkley says, of the anterior pituitary: "No nerve-*cells* are to be found in the substance of the organ, and all nerves belonging to it appear to be derived from branches of the carotid plexus." This indicates that nervous energy supplied by this organ to the adrenal system, while produced through the intermediary of the layer of sensitive cells in the partition between the two lobes (see page 960 for its description), is due to a *stimulating* influence other than that which prevails in the posterior lobe. In other words, while the iodine in organic combination in the thyroid secretion is the *normal* stimulus of the sensitive cell-layer,—and one of the many stimuli to which it responds,—the posterior lobe is made up of many types of neurons which depend upon the lecithin formed between their protoplasmic partitions for their functional activity.

The organs differ markedly and significantly in one respect, therefore: *i.e.,* in the fact that, while the whole of the anterior lobe is devoted to the one purpose of energizing the suprarenal center, the posterior is an aggregate of many centers. This indicates, it seems to me, that if the organ were a general source of energy for the whole bed of cranial nerves, irrespective of the individuality and purpose of each nerve, it would have been similar in general construction to its mate, the anterior lobe. That it tends to suggest that each group of neurons in the posterior pituitary body is a highly specialized center for a single class of nerves. Indeed, this is experimentally, though indirectly, sustained by Andreizen's researches. He could not have traced a direct nervous connection with the olfactory bulb and with the cerebro-spinal axis had the organ been a center for the production of energy intended to be diffused promiscuously in the central gray matter.

Again, the connection between the posterior lobe and the nervous system cannot be limited to the cranial nerves, since we have seen how intimate is the functional relationship in which afferent impulses obtain, between the middle brain and the entire motor system. Were the cranial nerves alone involved, the skeletal muscles would have to be omitted from the list of structures under the organ's control. As we have seen, removal of the middle brain abolishes all "bodily movements," as Foster puts it, "carried out by means of co-ordinate motor impulses, influenced, arranged, and governed by coincident sensory or afferent impulses."

Yet, how can the posterior lobe influence organs with which it has no anatomical connection? Thus, the most prominent motor paths, the pyramidal tracts, arise, in the cortex, from the upper two-thirds of the central convolutions, pass down behind the knee of the internal capsule, and then penetrate the middle third of the pes cerebri, then the pons and the medulla, and finally pass down the cord. Where is the connection with the posterior pituitary? When the tracts "emerge from the pons," says Edinger,[62] "their fibers form two large bundles in the ventral portion of the medulla,"—*i.e.*, in the regions of the middle brain,—where, as we have seen, not only all nerves endowed entirely or in part with motor properties—the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, and twelfth pairs—are represented either by their nuclei or by communicating roots, but also where *all nerves acquire certain vasoconstrictor*, i.e., *sympathetic properties*.

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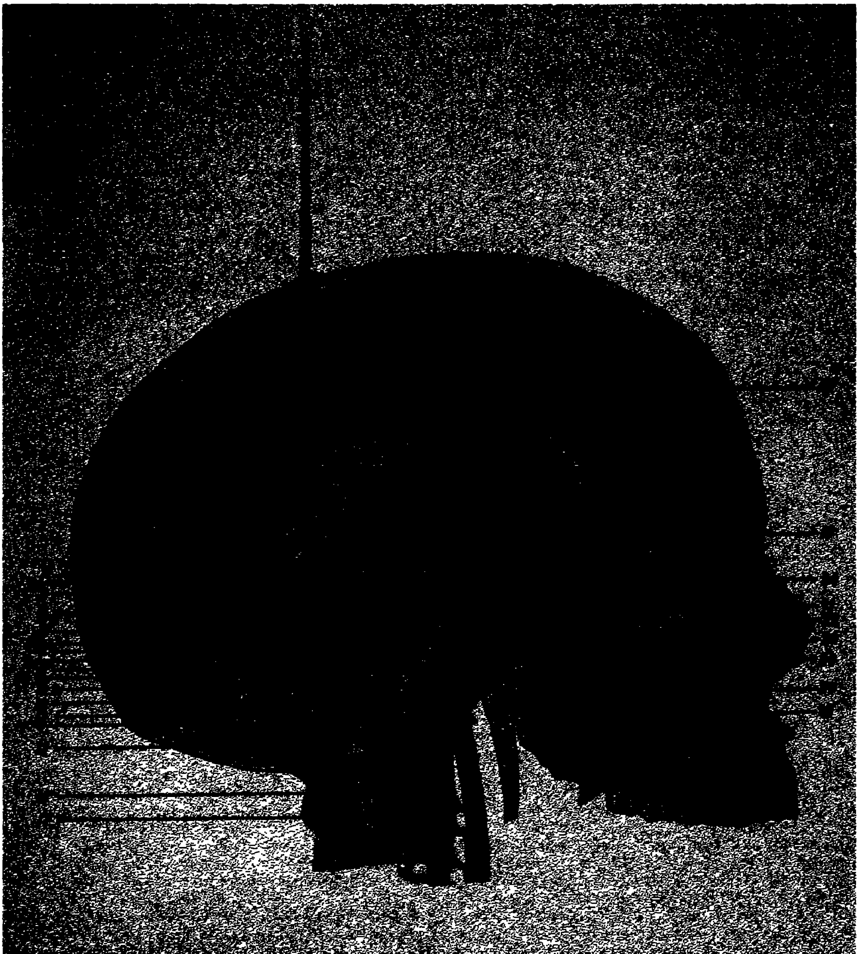
[62] Edinger: *Loc. cit.*

It becomes a question as to the manner in which the cerebrum is itself functionally governed, in so far as its somatic functions are concerned. In the light of the foregoing facts we are brought to the eminently logical conclusion that, in order to insure perfect co-ordination of the functional activity in all organs, a single structure is entrusted by Nature with this all-important rôle, *i.e.*, the posterior pituitary. *The cerebrum, as the organ of Mind, differs in no way from other organs*, from my viewpoint: *its circulation is also governed by the pituitary body* during its active and passive state: wake and sleep. I have previously referred to the fact that the medulla is only a transmitting center: a general station to which impulses from various directions arrive by the cord from below, by the commissures from the encephalic structures, and establish junctions with the several paths with which they are related. "The encephalon is a very complicated system of large and small continents of gray or central nervous substance," says Professor Duval, "communicating one with another and with the medulla by numerous commissures."

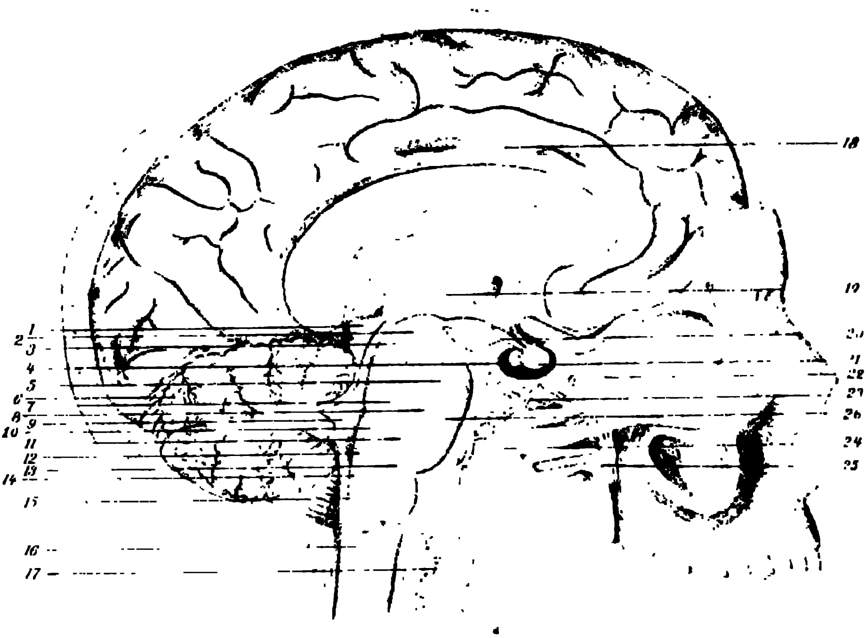
We have seen how absolutely independent of motor functions the hemispheres are, though volitional attributes enable them to *utilize* the motor system. Indeed, the experimental evidence adduced on this score is incontrovertible. But the same distinguished physiologist says: "The nerve-cells of the cord form in this organ a continuous central gray mass, extending from one extremity of the organ to the other. But, if the anatomist locates the superior limit of the cord on a level with the occipito-atloidian articulation, for the physiologist the cord extends into the interior of the cranium; it reaches to the aqueduct of Sylvius (the true origin of the motor oculi communis and patheticus) and even on a level with the third ventricle—the gray substance of the walls of this ventricle." We have seen that he also referred to its reaching up to the *sella turcica*. That it is *within* this bony structure that the main center of this vast mechanism—with its extensions and terminals, including the vasomotor fibers—lies, has been sufficiently emphasized. I feel, therefore, that I have good



THE POSTERIOR PITUITARY BODY AS GENERAL CENTER OF THE NERVOUS SYSTEM. (Sketch.)

Nervous Connections from the Posterior Pituitary Body [illegible] the [illegible] Ganglia, the Medulla [illegible] and the Cord.

[illegible]



THE POSTERIOR PITUITARY BODY AS GENERAL CENTER OF THE NERVOUS SYSTEM.

Showing Continuation from the Posterior Pituitary Body, of **the** Infundibulum, the Floor of the Third Ventricle, the Medulla Oblongata, and the Cord.

1, Corpora Quadrigemina. 2, Motor Oculi. 3, Patheticus. 4, Posterior Pituitary Body. 5, Motor Branch of Fifth. 6, Cerebellum. 7, Abducens. 8, Trigeminus. 9, Fourth Ventricle. 10, Glosso-Pharyngeal. 11, Facial. 12, Pneumogastric [Vagus]. 13, Auditory. 14, Hypoglossal. 15, Spinal Accessory. 16, Spinal Cord. 17, Spinal [illegible]. 18, Left Hemisphere. 19, Third Ventricle. 20, Infundibulum. 21, Anterior Pituitary Body. 22, Optic Nerve. 23, Carotid Plexus. 24, Gasserian Ganglion. 25, Spheno-palatine Ganglion. 26, Pons Varolii.

successively removed, the animal still shows, by characteristic agitations and *plaintive* cries, the pain it experiences when submitted to strong external excitations: *i.e.*, when its leg is squeezed with pincers or a bare nerve is excited. If the pons itself and the upper part of the medulla are now destroyed, the animal at once ceases to respond by similar cries and agitations." . . . . "An animal that has lost its pons has therefore lost *a center for the perception of sensitive impressions*." The gray ganglionic substance of the pons is, we have seen, a part of the central gray matter which begins in the posterior pituitary body: a fact which suggests that the latter may be the seat of functions now ascribed to this part of the pons.

Indeed, these instinctive involuntary acts are dominant in the entire phylogenetic scale even in vertebrates devoid of skull or brain: the amphioxus, for example, down to which Andriezen traced the structures which ultimately become the pituitary bodies. It is difficult to conceive of an *inciting* and *governing* efferent impulse from the posterior pituitary without an afferent impulse conveying to it the needs of the organ to be incited to activity and governed. Duval refers to weeping, for instance; tears, we have seen, are brought on by increased circulation and stimulation of the cellular elements of the lacrymal glands; what is this but functional activity enhanced by impulses to the posterior pituitary—if my previous conclusions are at all warranted?

True, we are dealing primarily with a mental phenomenon, but this only proves that afferent impulses may reach the posterior pituitary from the cortex of the hemispheres as they can from any organ. Nor is the act an instinctive one; but this fact also affords supporting testimony, since it tends to show that the organ is not only influenced by impressions of a purely reflex kind, or connected merely with organic life, but also by the highest form of nervous action: *i.e.*, mentality. What better evidence can we have of this than the violent cardiac action; the trembling; the involuntary excretion of urine, of fæces, of sweat; or even the sudden arrest of the heart, all of which phenomena may attend intense fear, and all due to loss of control *by the posterior pituitary*, under the violence of the mental impulses over . . . muscular tissue: cardiac, skeletal, cystic, intestinal, and sudorific? To this list I may add loss of control over all vasoconstrictors, since we have relaxation of the larger internal vascular trunks, central engorgement, in virtue of the principle—"vessels supplied with a muscular coat and capillaries are mutually antagonistic in contraction and dilation"—submitted in the earlier chapters and the mechanism of which we can now understand. Both antagonistic conditions are expressed in another symptom of fear: *i.e.*, intense pallor, the lividity of Asiatic cholera and, indeed, of the moribund. Truly instinctive, however, is the sudden cry or scream brought on by unexpected pain: evidently the result of an impulse to the posterior pituitary, since we again have a series of muscular actions of the chest, glottis, etc., which are necessary for the cry. Laughing, sneezing, coughing, and other kindred acts are all manifestations of motor activity; and so is vomiting the result of afferent and efferent vagal impulses, again with muscular structures as the mechanical factors and the posterior pituitary as inciting and governing organ.

And a striking proof of this is furnished by the fact that these manifestations of activity not only prevail in a frog deprived of its hemispheres, but that, if the animal is kept alive and in good health, signs suggestive of intelligence appear. "For days or even weeks after the operation," says Professor Foster, "there may be no signs whatever of the working of any volition; but, after the lapse of months, movements, previously absent, of such a character as to suggest that they ought to be called voluntary, may make their appearance. . . . Even in their most complete development such movements do not negate the view that the frog, in the absence of the cerebral hemispheres, is wanting in what we ordinarily call a 'will.'" Nor need they, for these so-called involuntary, instinctive acts are dominant even in vertebrates devoid of skull or brain: the amphioxus, for example, down to which Andriezen traced the structures which ultimately become the pituitary bodies.

That the posterior pituitary is a *discerning* organ, and one, at that, capable of simultaneously subserving many functions, seems very probable. Totally independent of the brain, *though its servant when need be,* it appears to me as the undoubted seat of the many centers—*i.e.,* for cardiac action, respiration, vasomotor action, sneezing, coughing, etc.—that have been located in the medulla oblongata. True, local disease or traumatism point to the "bulbar" areas concerned as "centers." But if the bulb is given the rôle which I believe it to fulfill, —*i.e.*, that of a secondary or rather subsidiary *consociating* organ,—it will become apparent that any lesion capable of blocking the multitude of afferent and efferent impulses that traverse it at all times and which represent the aggregate of the organisms inciting and governing energy must necessarily compromise life or the functions of an organ to which the blocked nerves are distributed.

I have expressed the belief that the posterior pituitary body is the primary co-ordinating center—so far unidentified as to central origin—of the sympathetic system. This view has not only been sustained by the analysis of the functions of the various organs, but it seems to me fully to coincide with established facts.

As Regards Efferent (Motor) Impulses.—It has been experimentally determined that all fibers that originate from roots in the *anterior* portion of the cord are *efferent: i.e.*, transmit motor impulses from the cord to the periphery. Section of these fibers causes: in muscles, paralysis; in glands, cessation of secretion; in vessels, dilation.

Interpreted from my standpoint, these morbid phenomena are accounted for as follows: As the *active* functional state of any organ is brought on, we have seen, by strictodilation of its arterioles, *i.e.*, constriction of their vasa vasorum (that attending the *passive* functional state), section of the nerve transmitting the constrictive impulses brings on the opposite of active function,—*i.e.*, paralysis,—or, if distributed to a gland, arrest of secretion. Although the same impulses serve to *incite* and *govern* the cellular activity of the organ, paralysis, muscular or glandular, is not due to the loss of these two functional attributes, since section of vagal efferent nerves, which only incite and govern the active functional state beyond tonic contraction, does not cause paralysis. The immediate cause of the latter is slowing of the blood-stream: *i.e.*, reduction of the supply of oxidizing substance. The cellular elements lose their mechanical energy and can no longer be incited to action and governed. The mechanical energy being due to the adrenoxidase present, it is traceable through the adrenal system to the *anterior pituitary body,* while the inciting and governing influence, being of cerebro-spinal origin through the anterior root severed, is traceable to the *posterior pituitary body.* That it is of central origin is shown by the fact that removal of the pituitary is followed by general vasodilation.

Control experiments are represented by the well-known facts that stimulation of an anterior root causes vasoconstriction and increased functional activity, and, if sufficiently strong, convulsive movements of muscles. The latter, as we have repeatedly seen, are due to excessive oxidation of the muscular elements—complemental testimony to the effect that inadequate oxidation is a primary source of paralysis or at least of functional inhibition.

I have previously shown that the bulbar vasomotor center and the cranial nerves that possessed motor properties occupied the same medullary region: the *upper.* As general motor nerves possess vasomotor properties, the reason for this is obvious. Again, we have seen that the cranial nerves which acquire motor properties by anastomosis were grouped in the *lower* portion of the medulla. The entire organ thus becomes a conductor for general motor impulses, whether transmitted by the cord (as indicated by the general vasodilation incident upon medullary section) or by cranial nerves.

Although this aggregate of motor areas in the medulla represents but radiating paths from a common center, the posterior pituitary lobe, present conceptions as to their distribution—whether to the extremities, the thorax, the cranial nerves, etc.—or their anatomical relations with the hemispheres—the cerebellum, etc.—are in no way modified. All we need to bear in mind, and as will be shown later, the sympathetic system is not an autonomous system of nerves, and that it is a subdivision of the general motor system originating, like all motor nerves, from the cord, while its impulses emanate from the pituitary.

Summarized, these facts—which will be supplemented by evidence in the second volume—suggest that, *while the medulla oblongata is an important consociating organ, its centers receive* *impulses from, and are controlled and co-ordinated by, the posterior pituitary body.*

Unlike the anterior lobe, which governs and sustains oxidation and metabolism through the adrenals, however, the posterior lobe is not necessary to life, since it is but a co-ordinating structure.

As Regards Afferent (Sensory) Impulses.—It has likewise been experimentally ascertained that all fibers that originate from roots in the posterior portion of the cord are *afferent: i.e.,* transmit sensory impulses from the periphery toward the cord. Section of these roots is followed by loss of sensation.

Interpreted from my standpoint, sensory impressions are similarly transmitted from all parts of the organism, and the one general sensory system supplies the needs of all. The nature of the impulse being governed by the specific cellular characteristics of the peripheral structures which receive the impressions, whether related to a special sense, general sensibility, variations of functional activity, etc., they all reach the posterior pituitary. That such is the case is suggested by the fact that, while frogs deprived of the hemispheres exhibit typical signs of continued co-ordination and sensation, removal of the bulb then causes them no longer to show these signs. This does not exclude the functions of subsidiary centers,—*i.e.,* reflex centers, ganglia, etc.,—which probably serve as accumulators of energy, and act in lieu of the posterior pituitary body unless the peripheral stimulation exceed their potential as to the efferent energy actively used. The law of generalization of Pflüger,—*i.e.,* propagation of (reflex) impulses to the medulla under excessive excitation,—which, according to my view, applies to the posterior pituitary, typifies the maximum effect produced under such conditions, and further demonstrates the connection between the periphery and the latter organ.

Control experiments are represented by the familiar results of stimulation of the dorsal roots, which causes augmentation of reflex activities and of conscious sensations. The reflex inhibition of functional activity of certain organs I have ascribed to excessive stimulation: in accord, therefore, with foregoing facts. This affords the complementary concordance required to place my conception of the functions involved on a solid foundation.

All these data suggest a postulate, the importance of which must be emphasized: *i.e.*, the identity of the posterior pituitary body as the center upon which all emotions, shock, etc., react, and as the organ which initiates the phenomena that attend the impressions thus produced.

That this organ is directly or indirectly connected with the cerebrum in all phenomena pertaining to intelligence, reason, and will, precisely as its motor functions—other than the purely automatic ones—may be dominated by these higher manifestations of nervous activity, need hardly be emphasized. "Sensory" in its broad sense, from my viewpoint, and refers to impressions received by all end-organs endowed with sensation, as previously stated. Whether these first reach the eye, the ear, the cutaneous surface, the gustatory papillæ, the olfactory area, etc., or be due to traumatism, surgical procedures, an abnormal mental state, such as attends fear, grief, or other emotions, etc., we are always dealing with molecular jarring of the posterior pituitary body: harmless when slight, pathogenic when sufficiently intense, but fatal when a certain limit is reached. Precisely as the current passed through the region by the Weber brothers inhibited the heart, so can fright, intense pleasure, or shock prove fatal by inhibiting the heart, but primarily by *jarring the posterior pituitary body*—or, speaking more correctly, by inducing excessive molecular vibration of its elements.

The maximum effect of shock thus becomes an arrest of nervous impulses through which function is sustained *via* the cerebro-spinal axis. This may well be illustrated by the description given by Professor Stewart of the "various phenomena which are grouped together under the name of shock" as exemplified by section of the cord. "When the spinal cord of a dog is divided,—*e.g.*, in the dorsal region,—all power—all vitality, one might almost say—seems to be forever gone from the portion of the body below the level of the section. The legs hang limp and useless. Pinching or tickling them calls forth no reflex movements. The vasomotor tone is destroyed, and the vessels gorged with blood. The urine accumulates, overfills the paralyzed bladder, and continually dribbles away from it. The sphincter of the anus has lost its tone, and the fæces escape involuntarily." I hardly need to emphasize the fact that we have here a summary of all the phenomena which attend loss of functional activity: of those, at least, I ascribe to the posterior pituitary body.

But this experimental section of the cord was also chosen as an example of the wonderful resources of nature when life's functions are to be preserved. "If we were to continue our observations only for a short time, a few hours or days," continues the author, "we should be apt to appraise at a very low value the functions of that part of the cord which still remains in connection with the paralyzed extremities. But these symptoms are essentially temporary. They are the results of shock; they are not true 'deficiency' phenomena. And if we wait for a time, we shall find that this torpor of the lower dorsal and lumbar cord is far from giving a true picture of its normal state; that, cut off, as it is, from the influence of the brain, it is still endowed with marvelous powers. If we wait long enough, we shall see that, although voluntary motion never returns, reflex movements of the hind-limbs, complex and co-ordinated to a high degree, are readily induced. Vasomotor tone comes back. The functions of defecation and micturition are normally performed. Erection of the penis and ejaculation of the semen take place in a dog. A man with complete paralysis below the loins and destitute of all sensation in the paralyzed region has been known to become a father (Brachet). Pregnancy carried on to labor at full term has been observed in a bitch whose cord was completely divided above the lumbar enlargement."

How can the return of functions—so far unexplained by physiologists—be accounted for? The foregoing data suggest that the pituitary should be the organ "shocked" by the operation. Moreover, removal of this organ, except after its gradual destruction by disease, produces identical effects. Indeed, the resumption by the lower and dorsal cord of its normal functions would not occur if the path from the pituitary to the adrenals had also been severed. As Goltz and Ewald have shown, animals deprived of their cord from the bulb down cannot keep warm, and even die of cold; but Ott found that this did not happen when the section was made below the fifth dorsal. As this is immediately below the region where the pituitaro-adrenal nerves leave the cord to enter the sympathetic chain and thence pass on to the adrenals, these results find their ready explanation: As soon as the posterior pituitary had recovered from the shock, it resumed its influence on the adrenals, the secretion of which, as previously shown, endows the hæmoglobin with its oxygenizing constituent. Metabolism—the life process—being resumed in the severed segment of the spinal cord, its normal functions returned.

It seems extraordinary to connect the adrenals—as I did in 1903 in the present work—with fright, anger, traumatic shock, etc.; and yet the recent experimental work of Cannon and de la Paz,[63] in the Harvard laboratories of physiology, has demonstrated that under the influence of such emotions in the cat the inferior vena cava contains an excess of secretion. Cannon and Hoskins[63a] also state in this connection: "The similarity between surgical shock and the condition of an animal after removal of the adrenal glands suggests that possibly in surgical shock the injury to large nerve trunks may discharge the adrenal glands to such a degree that they are unable to continue their normal functioning."

If to all this be added the fact that the manner in which violent emotions, fright, trauma, shock, etc., provoke various diseases, exophthalmic goiter, railway spine, and concussion, for instance, it seems probable that *the posterior pituitary body, as the most highly organized aggregate of somatic nerve-centers, is the organ upon which all shocks—physical,* i.e., *cerebral or traumatic—react.*

Illustrative also of the rôle of shock, physical and mental, in the production of disease is acromegaly. Fully 20 per cent. of these cases are due to some form of accident, often falls upon the head. Its syndrome, better than any other disease, shows, from my viewpoint, the relationship between the pituitary and the body at large. Hence its presence at the end of the present chapter.

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[63] Cannon and de la Paz: American Journal of Physiology, April 1, 1911.
[63a] Cannon and Hoskins: *Ibid.*, April and December, 1911.

ACROMEGALY: PIERRE MARIE'S DISEASE, AND GIGANTISM.

The first question that imposes itself in this connection is whether the pathogenesis of this disease of the pituitary body must be based upon the prevailing belief that this organ is a secreting gland or, as I believe, upon its identity as a coordinating center which includes, among its functions, that of governing the secretory activity of the adrenals and thyroid apparatus.

I have already urged that the prevailing opinion that the pituitary is a secreting gland has so far remained unproven, while every item of evidence brought in favor of this view can be shown to be questionable as such. The main argument in its favor is that extracts of its posterior lobe can produce vasomotor phenomena; but this fact loses its value in the presence of Wiesel's[64] demonstration that this lobe is rich in chromaffin substance, *i.e.*, in adrenal principle. That under these conditions its extracts should give rise to the same phenomena as the latter is plain. To enumerate these phenomena is to rehearse all those that were credited to the secretion of the adrenals in the second chapter by the many investigators cited therein. Thus, Mairet and Bosc[65] found in 1896 that subcutaneous injections of pituitary extract caused a rise of temperature which lasted a couple of hours. An intravenous dose produced marked myosis, slowing of the respiration, powerful cardiac beats, and hyperthermia as main signs, the animals recovering, however. Schäfer and Vincent[66] then found that pituitary substance raised the blood-pressure, and that this substance when applied to mucous membrane caused blanching, as is the case when a solution of adrenalin is applied. They also noted that in small mammals it caused, in toxic doses, paralytic symptoms which *they* also consider analogous to those caused by adrenal extracts. According to Jas. Barr,[67] pituitary extract actively produces arteriosclerosis, and it is also known to produce glycosuria. Finally, Hallion and Carrion, studying its therapeutic action, found that pituitary extracts "always produced their effects by raising the arterial tension." In other words, it awakens all the typical phenomena, physiological and pathological, to which the adrenal product gives rise.

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[64] Wiesel: International Clinics, vol. ii, 15th series, 1905.
[65] Mairet and Bosc: Arch. de physiol., p. 600, 1896.
[66] Schäfer and Vincent: Jour. of Physiol., vol. xxv, p. 87, 1899.
[67] Barr: Lancet, Nov. 13, 1899.

Twelve other general facts, covering a wide scope of research in the domain of various branches, submitted on page 510, also indicate that the pituitary is not a secreting organ.

Again, if the pituitary body were the source of an internal secretion its removal, as has been repeatedly done in recent years by Hochenegg, Cushing, and others for tumors, should prove harmful if not fatal, as is the case when the thyroid apparatus or the adrenals, which we *know* to be the source of internal secretions, are removed. But such is not the case. If, on the other hand, the pituitary is considered, with me, as a co-ordinating center supplied with subsidiary centers in the bulb, which centers could normally assume its functions gradually as the chief center is being destroyed, we can readily understand how a degenerated and useless pituitary can be removed with impunity.

Twenty-six years have elapsed since Pierre Marie identified acromegaly with the pituitary, and it must be admitted that the secretory theory has served but little if anything to elucidate its pathogenesis. Indeed, notwithstanding the painstaking labors of many distinguished observers, George Dock[68] could but write of it recently (1911): "Acromegaly is closely associated with disease of the pituitary body, but the alterations reported by various observers have been interpreted so differently that it is still uncertain just what the true relation is." The semeiology of the disease and its pathology have been raised quite to the high level of diseases that have had the benefit of centuries' analysis; but the relation between the seat of lesion and the clearly defined external phenomena of the disease still belong to the domain of conjecture. Will my interpretation of the functions of the pituitary body prove more fruitful in results? All that is claimed for it is that it offers a field for new lines of thought.

PATHOGENESIS AND SYMPTOMATOLOGY.—Tamburini[69] has shown, after an analysis of twenty-four cases in which autopsies had been made, that "in all *typical* cases of acromegaly a growth of the pituitary prevailed, but that there was, at first, hypertrophy of the gland, *with exaggeration of its functions,* and, later on, *abolition of these functions,*" a view in which Harlow Brooks,[70] after a painstaking study of the whole subject, concurs. These and other facts I will submit below have suggested the advisability of dividing the disease into two stages, the first representing the ascending period of the disease in the sense of exaggerated nutrition, terming it the *sthenic* stage, and to add thereto another stage representing the period of decline, as was done in other diseases of the ductless glands, namely, the *asthenic* stage. This will make it possible to identify the meaning of each symptom, and also, perhaps, to suggest more effective remedial measures than those now employed.

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[68] Dock: Musser and Kelly: "Practical Treatment," p. 853, 1911.

[69] Tamburini: Riv. Sper. di Fren., p. 559, 1894, and p. 414, 1895.

The characteristic phenomena of acromegaly have naturally established it as a disease of nutrition, as foundation for the many theories that have been advanced to explain its pathogenesis. To account for its symptoms, therefore, through organs such as the thyroid and adrenals, to which I have attributed such leading functions in oxidation and nutrition, must *a priori* seem, to say the least, reasonable. Again, the identity of the pituitary body as the starting point of the disease has been demonstrated by Marie and many other observers since. If, therefore, exaggeration of function is followed by abolition of function, another established fact, we have seen, we are brought to the logical conclusion that the diseased pituitary first excites the thyroid and adrenals, which, as I have shown; provoke hyperthyroidia and exophthalmic goiter, and also hyperadrenia, and that it subsequently depresses these same organs, bringing on, to a more or less marked degree, the opposite states: hypothyroidia, myxœdema, and Addison's disease or its milder prototype hypoadrenia. Interpreted from this viewpoint, then, the disease might be defined as follows:—

Acromegaly is a disease of nutrition, due to any condition, hyperplasia, neoplasm, etc., of, or any pressure upon, the pituitary body, capable of primarily exciting abnormally this organ, and then of progressively annulling its functions, and also, therefore, those of the organs it controls, viz., the adrenals and thyroid

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[70] Harlow Brooks: Arch. of Neurol. and Psychopath., vol. I, No. 4, 1898.

apparatus, whose combined secretions sustain tissue oxidation, metabolism, and nutrition. Its symptoms are, during the first stage: excessive tissue growth, merged with those of hyperthyroidia and hyperadrenia, and, during the second stage, with those of hypothyroidia and hypoadrenia.

No reference is made here to the other functions of the pituitary in order to restrict the morbid process to its main general cause.

The *sthenic* stage is replete with clinical evidence of the participation of the thyroid apparatus in excessive development of the body. There are several cases of acromegaly on record which, by showing in an exaggerated manner the involvement of the pituitary,—to the point of bringing on all the prominent signs of exophthalmic goiter,—clearly indicate the participation of the thyroid even in those cases in which such prominent phenomena do not appear. Thus, Lediard[71] exhibited a case before the Clinical Society of London, in which the accompanying goiter was sufficiently large to require operation. Neal and Smyth[72] also witnessed a case in which a parenchymatous goiter was present. Sometimes swelling of the neck, which develops into a goiter, is the first symptom observed, as in a case reported by Grove.[73] In these cases, which but exemplify many others on record, the goiter might, however, occur as an independent condition. But in many instances the full syndrome of exophthalmic goiter is present. Lancereaux[74] reported 5 such cases, and Murray[75] 2 out of 4 cases of acromegaly he had witnessed. Exophthalmus, tremor of the hands, and glycosuria were prominent features. Hinsdale,[76] in fact, found exophthalmus in 23 out of 130 reported cases—evidence of the frequency with which the major symptoms of exophthalmic goiter are present, and of the important factor the thyroid apparatus must represent in the pathogenesis of acromegaly.

As to the adrenals, we must not lose sight of the fact that we are dealing with the sthenic stage of the disease, *i.e.*, that in which both the thyroid apparatus and the adrenals are rendered

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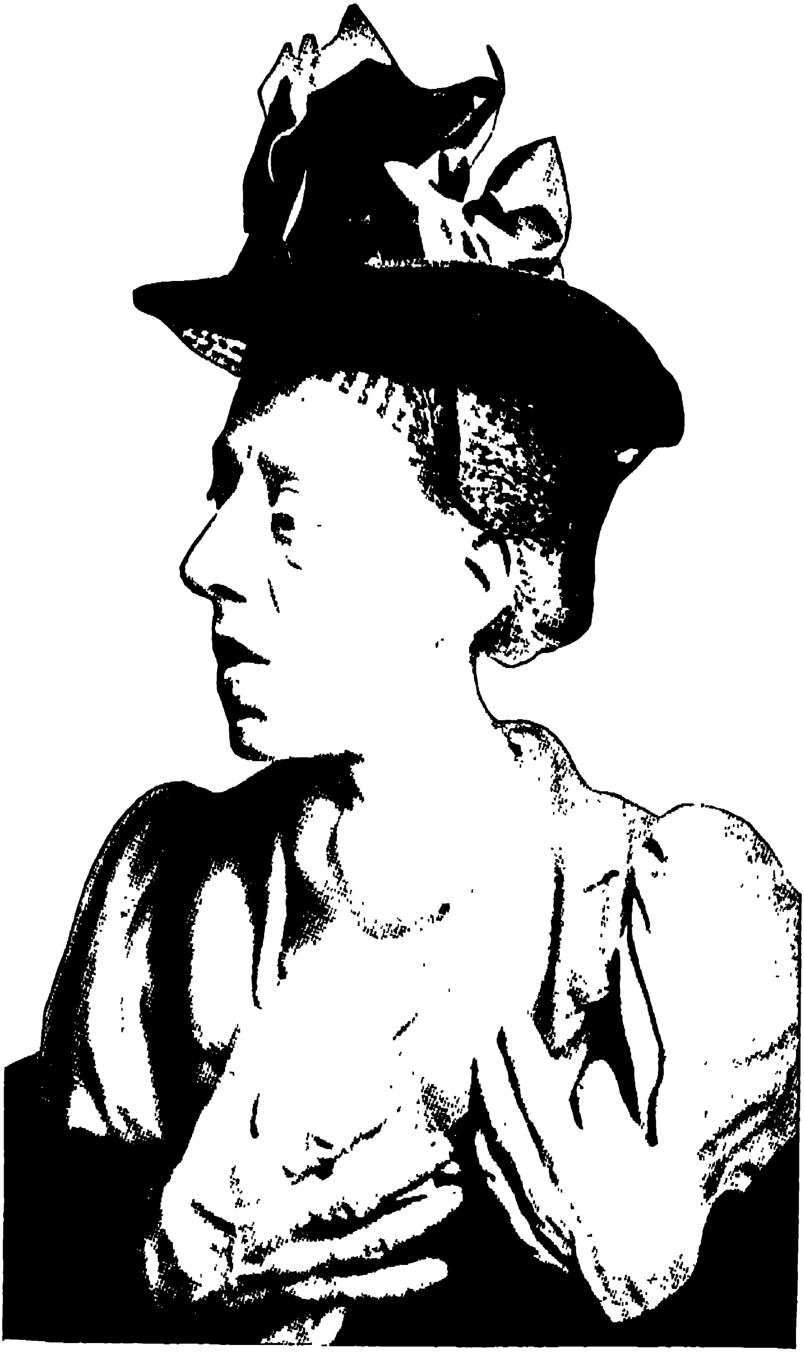
[71] Lediard: Brit. Med. Jour., April 4, 1903.
[72] Neal and Smyth: London Lancet, July, 1898.
[73] Grove: Bulletin Johns Hopkins Hosp., Sept., 1910.
[74] Lancereaux: Semaine médicale, June 24, 1896.
[75] Murray: Edinburgh Medical Journal, p. 170, 1897.
[76] Hinsdale: "Acromegaly," p. 23, 1898.



CASE OF ACROMEGALY, EXOPHTHALMIC GOITER, PHTHISIS, AND GLYCOSURIA. [illegible]

overactive by the irritated pituitary. Here, therefore, the connection is with excessive activity of the adrenals, such as adrenal hypernephromas furnish. Now, Owen Richards[77] describes such a case in a girl of 7 years, "who was as tall as a person of 20." Tileston and Wolbach,[78] referring to this type of cases, state that "they are obese and abnormally large for their age, a child of 5 years having the size and general appearance of a boy of 16 (Linser's case). Pigmentation of the skin may occur, but the color is more like that of a brunette than like the bronzing seen in Addison's disease. The intellect is dull and the disposition sullen. Appetite and sometimes thirst are increased, and vomiting is likely to be an obstinate feature" . . . As these phenomena occur as the result of an excess of an adrenal tissue, however, the body growth might only occur solely as an effect of such a surplus of adrenal secreting tissue; but that normal adrenals under stress—as they are in acromegaly—are capable of producing it, is well shown by the additional statement of Tileston and Wolbach's, that "in three instances (Otto,[79] Crecchio,[80] Marchand[81]) premature development has been associated with simple hyperplasia of the adrenal glands."

We thus have functionally overactive the two organs known to stimulate growth by their secretions: the adrenals, we have just seen, and the thyroid, as illustrated by its influence on body growth in the treatment of cretinism; and if, as Meige wrote: "Gigantism is the acromegaly of the growing period, while acromegaly is the gigantism of the period of completed development," these two organs, beyond doubt, account for the morbid growths. When to this we add the recognized fact that the thyroid apparatus influences calcium metabolism, we have all the factors necessary to trace the most characteristic phenomenon of the disease: the progressive enlargement of the bones and soft tissues, to its source. Marie restricted his conception of the disease to enlargement of the extremities (hence, ἄκρον, extremity, and μέγας, large), but, besides these, the bones of the skull, face, arms, and legs, the spinal column, scapulæ, clavicles, and the ribs are also caused to grow, increasing the stature in the young and building upon giants, but causing deformities (projection anteriorly and posteriorly of the thoracic cage—of which the double hump of Punch or Punchinello is the type—in some) in adults. The soft tissues over the entire body are no less overnourished; the enormous hands and feet, the hypertrophied muscles, which, notwithstanding their great bulk, are weak, and the hypertrophied heart, scalp, face, lips, tongue, penis, etc., bear witness to this fact.

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[77] Richards: Guy's Hospital Reports, vol. lix, p. 217, 1905.

[78] Tileston and Wolbach: Amer. Jour. Med. Sci., June, 1908.

[79] Otto: "Path. Anat.," p. 139, 1816. Cited by Tileston and Wolbach, *Ibid.*

[80] Crecchio: Wien. med. Presse, N. 30, p. 763. Cited by Tileston and Wolbach, *Ibid.*

[81] Marchand: Beitr. zur Wissensh. Med., B. 1, 1891. Cited by Tileston and Wolbach, *Ibid.*

Side by side with this morbid growth we witness, more or less marked, the other phenomena of thyro-adrenal activity. There is abnormal demand for food; indeed, bulimia is considered by Hinsdale[82] as "one of the characteristic signs of acromegaly"—a fact which points to exaggerated metabolism. Thirst is also marked in some cases "out of all proportion to even the extraordinary size of the subjects," says the same writer, a symptom which he connects "with the glycosuria present in many cases." But here, also, we are dealing with a prominent symptom of exophthalmic goiter, and also of adrenal overactivity, since, as shown by Blum, Herter, Croftan, and others, injections of adrenalin produce it. So marked, in fact, is the connection between acromegaly and exophthalmic goiter and glycosuria that it has attracted attention. Lorand,[83] for instance, observed, independently of my views, that there was an intimate relationship between these disorders; that similar conditions: fevers, traumatisms, shock, etc., brought all three on; that polyuria, polydipsia, polyphagia were also met in all. In all three also more or less pronounced swelling of the thyroid occurred, having himself noted it in diabetes. Launois writes in this connection: "Whether we adopt the view of Loeb, involving pressure changes, or that of Sajous, relative to nervous irritation [transmitted to the thyroid, adrenals, etc.], however, the presence of an intermediary is further required for the production of glycosuria. According to some, this intermediary factor is the pancreas; in the opinion of Gilbert and his followers, it is the liver which, under these conditions, becomes functionally overactive; according to Sajous, it is the adrenals, to which he traced nerves from the pituitary." Here, again, my views harmonize those of others: the adrenal secretion, by enhancing general metabolism, increases the functional activity of the pancreas and thereby the production of amylopsin; the hepatic glycogen is then converted by this ferment into glucose at an abnormal rate, producing glycæmia and glycosuria. Hence, it is by exciting the adrenals that the pituitary in acromegaly causes glycosuria. The circulatory phenomena include, we have seen, tachycardia where other signs of exophthalmic goiter prevailed. Others have noted a "paradoxical acceleration of the pulse." The "frequent and copious sweating," the tremors, the cramps, paræsthesias, tingling, shooting pains, due to circulatory disturbances in the neurons, sensory endings, etc.; dyspnœa, the anomalies of tastes, the tinnitus aurium, are all symptoms of acromegaly common to exophthalmic goiter. Both often give a history of rheumatic pains and occasionally symptoms of unbalanced mind, especially delusions of fear or maniacal excitement. Conversely, in both diseases the patient may lapse into a condition of melancholia. In both, also, are witnessed the brand of adrenal overactivity, a swarthiness, or dirty yellowish-brown hue of the skin, more marked in some parts than others.

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[82] Hinsdale: *Loc. cit.*, p. 27.
[83] Lorand: La Presse médicale, Sept. 19, 1903.

Passing to the *asthenic* stage, the connection with myxœdema as to failure of thyroid functions, and with Addison's disease as to adrenal insufficiency, is quite as clearly defined. "Myxœdema may form part of the hypophysial syndrome," writes Launois. "From the observation of Norman Dalton[84] to that of Sainton and Rathery[85] a large number of cases have been reported which support the view that this combination can occur."

The functional relationship between the pituitary and the thyroid is well shown by the case of myxœdema reported by Sainton and Rathery, just referred to, in which the pituitary had been destroyed by a malignant growth, while the thyroid, adrenals, and ovaries were atrophied. Here the period of growth of the tumor had evidently caused excessive activity—hyperæmia—of the other organs and finally their functional destruction by atrophy, with myxœdema as a result. Other cases of the latter in which the pituitary was destroyed have been reported.

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[84] Dalton: Lancet, Nov. 6, 1897.

[85] Sainton and Rathery: Société médicale des Hôpitaux, May, 1898.

Strikingly suggestive in this connection is a case of myxœdema reported by Adami,[86] in which there was cancer of the pituitary, while the thyroid was normal. This shows plainly that it was to the absence of the impulses from the pituitary that the hypothyroidia was due. When, therefore, in acromegaly, the pituitary loses, by gradual degeneration, its power to excite the thyroid, hypothyroidia occurs, while the general tissue hypertrophy remains over from the sthenic period. The general signs of exophthalmic goiter are then gradually replaced by those of myxœdema, though the symptom-complex of the latter is somewhat obscured by the physical changes remaining over from the first stage; still, cases of acromegaly have been reported in which the myxœdematous symptoms were sufficiently marked to warrant the conclusion that the two diseases were associated. Lyman Greene,[87] Auerbach,[88] and others have reported such cases.

The phenomena of hypothyroidia and its progressive form myxœdema both include, we have seen, hypothermia. "A no less singular manifestation," writes Launois,[89] referring to acromegaly, "is lowering of the internal temperature, which, in a patient of Bartels, remained for weeks at a time between 34° and 36° C. ($93^{1}/_{5}$° and $96^{4}/_{5}$° F.) without the supervention of any sign of collapse. The same phenomenon has been witnessed by Petrina. In a case reported by Götzl and Erdheim,[90] the temperature fluctuated for three weeks between 35° and 36° C. (95° and $96^{4}/_{5}$° F.), later falling to 33° C. ($91^{2}/_{5}$° F.) It would be rather difficult at the present time to explain the origin of such disturbances," continues Launois; "we shall merely point out their similarity to the phenomena observed in myxœdema, in which disorder the temperature often fluctuates between 33° and 35° C. ($92^{4}/_{10}$° to 95° F.) and sometimes even falls below these figures." This symptom is no paradox when interpreted from my viewpoint, since, as I have shown, the pituitary governs the thyroid apparatus, while the adrenals, in turn, sustain tissue oxidation, and therefore the body heat.

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[86] Adami: Trans. Cong. of Amer. Phys. and Surg., p. 114, 1897.

[87] Lyman Greene: N. Y. Med. Jour., Oct. 21, 1905.

[88] Auerbach: Wiener klin. Woch., Feb. 10, 1907.

[89] Launois: Monthly Cyclopædia and Medical Bulletin, Jan. and March, 1911

[90] Götzl and Erdheim: Zeitschr. f. Heilkunde, vol. xxvi; Intern. Med., p. 373, 1905.

"Unusual sensitiveness to cold," mental and physical torpor, and marked asthenia are also typical signs of hypothyroidia and hypoadrenia approximating Addison's disease. Facial œdema and even the moon face of hypothyroidal infantilism may be witnessed, as in Glaser's case,[91] though the deformities of the face, the prognathism, the projecting brows, mainly due to the osseous overgrowth of the sthenic stage, tend to conceal the myxœdematous signs in this region. There is often marked accumulation of fat, giving no œdematous pitting, and presenting the resistance to pressure as in myxœdema. This can evidently be of pituitaral origin; in a case reported by Madelung,[92] for example, a shot in the infundibulum was followed by marked obesity. Indeed, Fröhlich and Launois have elaborated syndromes, since sustained by numerous cases, in which adipose overgrowth is directly connected with neoplasms of the pituitary. There is good ground for the belief also that Dercum's disease, adiposis dolorosa, is primarily due to disorders of the pituitary. That thyroid gland is used as a remedy for obesity is known to every one; that obesity should occur when the thyroid apparatus is rendered deficient through inhibition of its center—the pituitary —by disease is self-evident.

Dilated veins, as in the infantilism of hypothyroidia, are commonly observed in acromegaly, though these may occur as a remnant of the sthenic stage. Suppression of sexual desire and impotence and amenorrhœa, rheumatic pains, neuralgia, are also common, as in hypothyroidia. A painful form has been identified which "may assume," says Launois, "the rheumatoid type when it becomes localized in a certain group of joints"—a sentence which reminds us vividly of the labors of Léopold-Lévi and de Rothschild, referred to under hypothyroidia. As in myxœdema we may also meet with various forms of delirium, delusions of persecution, mystery, and the manic depressive psychoses, and even with epileptic seizures. These are mainly due, as I have shown, to the accumulation of toxic wastes in the blood incident upon the inhibition of the antitoxic functions—

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[91] Glaser: Virchow's Archiv, B. cxxii, p. 389, 1890.
[92] Madelung: Langenbeck's Archiv für klin. Chir., lxxiii, p. 1066, 1904.

a result, in turn, of the deficient activity of the three organs which, from my viewpoint, take an active part in the process, the pituitary, the thyroid apparatus, and the adrenals.

The implication of the adrenals in acromegaly has been referred to in connection with the sthenic stage—that of overgrowth. In the asthenic stage we witness the effects of their functional decadence. "Small freckles are frequent," writes Pirie,[93] referring to a personal case; "patches of a yellowish bronzing occur on the face, the chest, and the insides of the thighs. (Motais describes a bronzing such as occurs in Addison's disease.) . . . The patient suffers from a brownish seborrhœa, especially troublesome in the scalp. The hair is thick and coarse. Palpitation and fainting fits occur often. Dyspnœa and asthmatic-like attacks occur, during which the patient has to sit up in bed and fight for her breath," attesting to marked insufficiency of the adrenals in the respiratory process. Harlow Brooks[94] also writes, "macroscopically, the skin in these areas is considerably thickened; the surface is rough and often fissured. A general brownish pigmentation is present in the average case, which, at times, strongly resembles that found in Addison's disease." But the signs of myxœdema are again apparent in the remark by Pirie, that the skin of the eyelids was "thickened and puffy," there being also increased lachrymation and "a colloid secretion between the eyelids"—the typical "watery eyes" of myxœdema.

The symptoms that belong to the domain of the pituitary proper, *i.e.*, those which are not brought about through the agency of the thyroid and adrenals, are the ophthalmic disorders, including progressive amblyopia, amaurosis, hemianopsia, etc., the result in turn of pressure by the enlarged pituitary upon the optic tracts, the chiasm, optic nerves, etc. That the headache, sometimes extremely severe, from which these patients may suffer is also due to pressure is probable, though we must remember that it may also occur during the early or sthenic stage of the disease, and may then be due to increased intracranial tension.

PATHOLOGY.—The prevailing view, at the present time, is that of Marie, which ascribes the disease to a secretion of the gland. We have now seen, however, that there is considerable evidence to the contrary, *i.e.*, in favor of my own view, that it is through the adrenals and thyroid mainly that the characteristic phenomena of the disease are produced. Marie's original idea that the disease is due to disease of the pituitary is strongly sustained by my views, however, though still a matter of doubt among a few observers.

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[93] Pirie: London Lancet, Oct. 5, 1901.
[94] Brooks: Archives of Neurology and Psychopathology, vol. 1, No. 4, 1898.

An important feature of the whole question is the predilection of the pituitary body for sarcoma, though, as suggested by Tamburini, Benda, Mendel, and others, many of these sarcoma-like tumors, on close histological differentiation by means of appropriate stains, proved to be examples of hyperplasia or adenoma, in which the destructive process does not proceed with as great rapidity unless the adenoma be malignant, which is frequently the case. This accounts for the fact that in many cases, particularly in women, the progress of the disease seems to be rapid, the asthenic stage, that characterized by hypothyroidia and hypoadrenia, coming on before the typical acromegalic changes and overgrowths have had time to advance materially. This probably corresponds with Parona's figures, which indicate that sarcoma or adenosarcoma is present in 64.5 per cent. of all cases.

That adenoma of the pituitary frequently occurs without giving rise to signs of acromegaly, or in fact to any symptoms, has been shown by Lowenstein. But we must not overlook the fact that many faces among the multitudes show marked evidences of overactivity of the pituitary at a given time of their existence. I have had occasion to treat a young man 6 feet 2 inches tall, in whom the prominent orbits, nose, and chin clearly indicate temporary hyperactivity of the pituitary. The same phenomena, though far more marked as to facial deformities than in the preceding case, were also observed in an average-sized woman by Léopold-Lévi, who pointed her out to me at the Rothschild clinic in Paris.

That children's diseases are frequently the source of temporary hyperplasia of the anterior lobe of the pituitary, I have no doubt. This sustains the personal view, treated at length in the second volume, that this lobe and the pars intermedia are mainly concerned, as a sensory organ, with the defense of the organism at large against disease.

TREATMENT.—Launois, referring to the cases in which Hochenegg removed the pituitary, states that "the progressive retrogression of the manifestations of acromegaly witnessed after excision of hypophysial tumors affords an argument of the first importance in favor of the theory of glandular hypersecretion." From my viewpoint, it affords a no less strong argument in favor of my view, since by removing the pituitary Hochenegg arrested the cause of the overstimulation of the thyroid apparatus and adrenals, to which the disease is due. Indeed, the latter view is the stronger, since the actual existence of a secretion from the pituitary is still a matter of conjecture, while the existence of the thyroparathyroid and adrenal secretions is beyond question.

The treatment of the disease has been necessarily restricted to symptomatic measures, and to the promiscuous use of organic preparations. The foregoing pages indicate that such should not be the case, and that, whatever use is made of the latter, they should always be carefully adjusted to the *stage* in which they are indicated. As stated by Dock,[95] "pituitary glands and extract have not produced definite improvement. The same may be said of thyroid treatment which has often appeared to make the symptoms worse." It is self-evident that in cases in the sthenic stage with the hyperthyroidia approximating, if not actually reproducing, exophthalmic goiter, and the blood already replete with thyroid secretion, the addition of thyroid gland to it cannot but prove harmful. But in a case such as Sears's,[96] in which the asthenic stage—which may appear early in women—was present, with signs of hypoadrenia, a puffy and mask-like face, dry and coarse hair, etc., with brown patches and asthenia denoting hypoadrenia, especially where, as the author specifies, "the thyroid could not be felt," considerable benefit can be obtained under thyroid treatment. In the sthenic or first stage, especially where the signs of exophthalmic goiter are marked, the treatment for that disease (see page 229) is indicated. The use of coal-tar products, it includes, is known in fact to afford considerable relief of the most distressing symptom of acromegaly, intense headache. Acetanilid and antipyrin, and also aspirin, have been considerably used for this purpose.

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[95] Dock: *Loc. cit.*, p. 854.
[96] Sears: Boston Med. and Surg. Jour., July 2, 1896.

With respect to the therapeutic value of pituitary extract a case reported by Rolleston was greatly improved by pituitary and thyroid extracts combined. But the author observed that the superficial resemblance of acromegaly to myxœdema seemed to justify the administration of thyroid extract, pituitary extract alone having failed to effect any improvement. The patient neglecting the treatment, ultimately died, the autopsy revealing a sarcoma of the pituitary—a type of growth which rapidly brings on the asthenic stage.

As to the use of pituitary alone in the asthenic stage, it has been found of value in some cases as a palliative for headache,[97] but Rénon and Delille[98] found, in a woman who showed clear symptoms of hypothyroidia, that it aggravated the acromegalic signs, including the deformities of the face, hands, feet, etc. Yet, in similar cases, the simultaneous use of thyroid has proven of value. The solution of this enigma was furnished by Rolleston[99] when he said that "the apparent success obtained from the administration of the combined extracts was in reality due to the thyroid extract." On the whole, all this indicates that, as soon as any sign of hypothyroidia or myxœdema appears, the treatment for the latter disease (see page 192) should be instituted.

In the light of the facts submitted under the heading of pathology, particularly those which refer to arrest of the morbid process, there is ground for the hope that appropriate remedies may further such a result. Until our hopes are fulfilled, however, operative measures, such as those introduced by Hochenegg in Europe and admirably developed by Cushing in this country (see his recent volume[100]), should be resorted to where remedies do not check the lethal trend.

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[97] See chapter xii, this volume; article "Pituitary Organotherapy."
[98] Rénon and Delille: Le Bulletin médical, June 24, 1908.
[99] Rolleston: Brit. Med. Jour., April 17, 1897.
[100] Cushing: "The Pituitary Body and its Disorders," Philadelphia and London, 1912.

CHAPTER XI.

THE INTERNAL SECRETIONS AND THE LEUCOCYTES IN IMMUNITY AND FEVER.

THE ADRENAL SYSTEM AS THE FOUNDATION OF IMMUNITY.

To understand the *vis medicatrix naturæ,* i.e., nature's way of antagonizing disease, and learn how to enhance her resources when these fail has increasingly imposed itself as the goal for which we should strive. So concordant is the thought, in fact, with our highest aims as physicians and humanitarians that it may be said to have seen light at the very dawn of medicine, and to have grown apace with time. Indeed, twenty-three centuries ago Hippocrates[1] taught: "It is to the efforts of nature that the attentive and able physician looks for guidance." Galen[2] was no less affirmative when he wrote: "Nature having originally formed the body must, when disease assails it, restore health." Today, the most virile trend of modern thought is a corresponding principle, that conveyed by the term "immunity." Whether we seek to identify the nature of antibodies, the process through which they are caused to appear in the blood, or the manner in which they and the phagocytes oppose infection, we are but following the path opened by the father of medicine 400 years before the Christian era.

We have now learned through the painstaking labors of a host of investigators that our organism is supplied with autoprotective substances; but, so far, the identity of these substances has not been revealed by them. Even Ehrlich's theory has failed in this particular. His side-chain theory, notwithstanding the many collateral facts the labors devoted to it have brought out, has remained but a clever figment of imagination in so far as the side-chain feature itself is concerned—a pure assumption the truth of which he is yet to demonstrate, notwithstanding the many years it has been most carefully studied.

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[1] Œuvres médicales d'Hippocrate, ed. Foës, ii, p. 195, 1801.

[2] Galen: "Contra Julianum."

Nor have the sources of the various substances which take part in the immunizing process so far been identified. Ehrlich hypothetically attributes this rôle to the tissue-cell, but, even granting that this be so, we are only driven back—unless we remain with him within the field of conjecture—to the necessity of showing whence these cells obtain their immunizing bodies, his so-called receptors. This he has failed to do, along with all other investigators in the same direction, because, in my opinion, he and they have overlooked the one field which, experimentally and clinically, offers the only solid foundation for a profitable analysis of the question, that of the ductless glands. Brown-Séquard, Langlois, Abelous, Charrin, Albanese, Zucco, and many others, we have seen, have laid stress on the antitoxic functions of the adrenals, while Vassale, Gley, Fano, and Zanda, and many other investigators and clinicians have urged a similar rôle in respect to the thyroid and parathyroids. This applies equally well to the pituitary body, according to Marie, Guerrini, Gemelli, and others. We thus have a series of organs found *experimentally and clinically* to protect in some way the body against intoxication. Is it not logical to conclude that they claim attention as the more likely to furnish the factors for a solution of this all-important problem?

Prompted by these indications, I advanced the view in the first edition of the present work (1903) that the body was supplied with *an immunizing mechanism*. I showed that the adrenals and the thyroid were the sources of two substances regarded by pathologists as prominent agents in the immunizing process, but the source of which they had not identified, and that the secretory functions of these organs were governed by a center located in the pituitary body. I suggested, moreover, that it was probably by exciting this center that various familiar drugs, mercury, for instance, and certain toxins, tuberculin, Coley's toxins, and the like, produced their beneficial effects. The eight years that have elapsed since these views were advanced have served only to strengthen them.

The identity of this mechanism suggests itself in view of the details already submitted in the chapters upon the adrenals, the parathyroid apparatus, the pituitary body, and the kidneys. But to facilitate the discussion of the subject, I will merely recall that, interpreted from my viewpoint, the functions of these organs, both physiological and defensive, are as follows:—

Adrenals.—These organs supply a secretion which, on reaching the lungs, absorbs the oxygen of the air and becomes a constituent of hæmoglobin—its albuminous constituent. It is, as such, taken up by the red corpuscles and secreted by these cells as droplets (the so-called "blood-platelets") in all parts of the body, including the *blood-plasma* itself. The purpose of this albuminous hæmoglobin, which I have termed "adrenoxidase," is to supply oxygen to the tissues and to the blood. Important in this connection, however, is that this adrenoxidase gives the reactions and presents other characteristics of a familiar agent in the classic immunizing process, the *immune body* or *amboceptor.*

The active participation of the adrenal secretion in the defensive function suggests itself when the connection between oxidation and fever is recalled. Adrenoxidase being the active agent in all oxidation processes, and being capable of raising the temperature, we have a clue to the identity of one of the most important of the symptoms we meet on all sides, and the actual nature of which has not, so far, been explained, namely, *fever.* Indeed, as stated by Lazarus Barlow[3]: "Even if we grant that fever is beneficial, we are completely ignorant of the manner in which it acts."

We may speak of neurogenic fever caused by injury to the corpora striata; of aseptic fever due to crushed tissue; of infective fever caused by certain pathogenic organisms or their toxins, or of hyperthermia, and of the nature of the substances that are oxidized, but the identity of the oxidizing agent, the *deus ex machina* in all these types, has remained obscure. This is the feature of the problem which, from my viewpoint, the adrenal secretion, converted in the lungs into adrenoxidase, supplies.

Barlow writes, moreover: "Experiment seems strongly to support the view that hyperthermia has a curative action, and thence it is but a short step to considering fever as beneficial, and as evidence of the setting in motion by the organism of one of its defensive mechanisms. And certainly in pneumonia, erysipelas, cerebrospinal meningitis, typhoid fever, the prognosis is better if the patient's temperature is moderately high than if it is definitely low." Now, we have seen by the labors of Albanese, Abelous and Langlois, Charrin, Oppenheim, and others that the adrenals also enhance the defensive power of the body, thus combining the production of fever with the beneficial action. That Halpern[4a] regards adrenalin as an antigen also suggests some immunizing functions.

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[3] Barlow: "General Pathology," 2d ed., p. 435, 1904.

Thyroparathyroid Apparatus.—The thyroid gland and the parathyroid glandules, which constitute this apparatus, produce secretions which, on passing out of the lymphatics (into which they are secreted), enter the left subclavian vein, and become merged into a single substance. Passing then into the blood of the superior vena cava, this secretion is carried to the lungs, and on reaching the air-cells is taken up by the red corpuscles—along with the oxygenized adrenal secretion. A salient feature of the immunizing process appears in this connection, viz., the thyroparathyroid product is also secreted by the red corpuscles into the blood and tissues, and by acting directly upon the phosphorus which the nuclei of all tissue-cells, pathogenic organisms, etc., contain, increases their inflammability, *i.e.*, their sensitiveness to oxidation. As such, it acts both as *opsonin* and *agglutinin*.

The thyroparathyroid secretion taking part in tissue oxidation with the adrenal product, it becomes also, logically, a normal participant in the production of fever. Now, this is so striking a feature of thyroid functions that the thyroid gland has been associated with the production of fever by Lorand and other authorities on the ductless glands. Lorand[4] urges in this connection the various manifestations of the febrile state, elevation of the temperature and the sensation of heat observed in Graves's disease, due, as is well known, to excessive activity of the thyroid and many other phenomena peculiar to the febrile state. "Both in Graves's disease and fever," he writes, "there is an augmentation of the processes of oxidation." Again, as previously shown, thyroid feeding causes febrile phenomena, *i.e.*, a rise of temperature of several degrees, both in man and animals, as shown by the researches of Chantemesse and Marie, Ballet and Enriques, Bourneville, and others; it increases the intake of oxygen and the output of carbonic acid, the output of sodium chloride, phosphoric acid, etc. Finally, operative or morbid arrest of thyroid functions causes hypothermia.

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[4] **Lorand:** Lancet, Nov. 9, 1907.
[4a] **Halpern:** Arch. f. exper. Path. u. Pharm., Oct., 1913.

Once more, and in keeping with Barlow's remarks concerning the beneficial influence of fever, do we find the thermogenic properties of the thyroid associated with marked defensive or immunizing activity. Besides the evidence to this effect I have already offered (see page 163) may be mentioned the protection it affords against toxic products of protein decomposition noted by Breisacher[5]—as far back as 1889, and by Blum,[6] Galeotti, and Lindemann[7]—and others. The increased vulnerability of myxœdematous subjects to infection, the rapidity with which thyroidectomized animals succumb to practically any infection that happens around are now familiar clinical facts. In his recent work, Swale Vincent[7a] states that "it may be supposed that the function of the internal secretion is to prevent poisoning by the products of body metabolism or by infections from without." My opinion that the thyroparathyroid product is what Wright has termed "opsonin" has been sustained, we have seen, by the investigations of Marbé, Malvoz, Stepanoff, and others.

THE PITUITARY BODY AS THE SEAT OF THE IMMUNIZING CENTER.—Considered in connection with immunity only, the pituitary body contains, from my viewpoint, a center—the immunizing center—located in the pars intermedia (between the two lobes) and connected with the adrenals and the thyroparathyroid apparatus by nerves. Through these nerves the immunizing center governs the functional activity of these two sets of organs, and, therefore, the production of adrenoxidase (amboceptor) and of thyroiodase (opsonin and agglutinin), besides general oxidation. As such, the immunizing center is also the heat of *fever* center, the febrile state indicating that one or more poisons are present in the blood which this dual center is antagonizing through its militant agents, the thyroparathyroid apparatus and the adrenals—and also indirectly, as we shall see later, through the phagocytes.

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[5] Breisacher: Arch. für Anat. u. Physiol. Supp., p. 509, 1889.

[6] Blum: Archiv f. d. Ges. Physiol., p. 617, 1902.

[7] Lindemann: Virchow's Archiv, p. 202, 1897.

[7a] Swale Vincent: "Internal Secretions and the Ductless Glands," p. 352. London, 1913.

To interpret this process intelligently, I will submit, as was done in the cases of the adrenals, the thyroparathyroid, and the pituitary, an outline of the main features of the evidence I have to offer, referring the reader to the second volume for a detail study of the whole question.

Of fundamental importance in this connection, is that

The pituitary body of all animals, from mollusks to man, contains a sensory organ which structurally resembles the nasal olfactory membrane.

Julin[8] urged, in 1881, that in ascidians the subneural gland (conjoined to the nerve ganglion which I assimilate to the posterior or neural lobe) was the ancestor of the pituitary body of vertebrates. Lloyd Andriezen[9] confirmed this view after a comprehensive study of the organ, from amphioxus to man. Personal work in the same line led to a similar conclusion. Now, at least as low down as mollusks there exists in the corresponding location a patch of epithelium, which Spengel has termed "the olfactory organ," and Ray Lankester[10] the "osphradium." Unaware of the connection between this structure in ancestral forms and the pituitary, Peremeschko,[11] Müller,[12] and also Cadiat[13] described a cleft between the two lobes of the latter organ, the walls of which they found to be lined with epithelium. The structure of this epithelium was only made clear, however, when the Golgi method was available. Gentès[14] then found that it was merged in the partition (the *pars intermedia*) separating the two lobes, and that it contained elongated nerve-cells which sent their neuraxons into the posterior lobe, and thence to the base of the brain. According to Gentès, these cells recall exactly the sensory elements of the nasal olfactory membrane. Caselli also found sensory elements in the pituitary of higher animals, while Boeke[15] and Gemelli[16] discerned them in the pituitary of fishes. A personal distinctive study of this organ from the true olfactory apparatus has shown, moreover, that the former could be traced down to lower forms, gradually receding in importance until the patch of epithelium "supplied with a special nerve and ganglion," as Ray Lankester describes it, in mollusks is reached.

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[8] Julin: "Recherches sur l'organis des ascides simples," Arch. de biol., ii, pp. 59, 211, 1881.

[9] Lloyd Andriesen: British Medical Journal, January 13, 1894.

[10] Ray Lankester: Article Mollusca, in Encyclopædia Britannica, 9th ed., xvi, p. 636.

[11] Peremeschko: Virchow's Archiv, xxxviii, p. 329, 1867.

[12] Müller: Jenaische Zeit. f. Naturw., vii, p. 327, 1873.

[13] Cadiat: Anatomie générale, cited by Guépin, Tribune méd., December 10, 1891.

[14] Gentès: C. r. de la Soc. de biol., lv, p. 100, 1903.

Suggestive in this connection, as a feature of the immunizing process, is that

In ancestral animals the "test organ" serves to test the purity of the sea water ingested by them.

Spengel's olfactory organ, Ray Lankester's osphradium, has for its purpose, according to zoölogists, to test the respiratory fluid. In amphioxus, the lowest of vertebrates, similar protection is afforded by what Willey[17] describes as a "vestibule richly provided with sensitive cells," and by Andriezen as a "nervous organ" which "serves to test the quality of the water which passes over the respiratory organ."

That a corresponding autoprotective function exists in the higher animals, including man, is not only sustained by considerable evidence, but a solid foundation for the whole scheme is afforded by the fact that the blood of these higher animals is the physiological and qualitative homologue of sea water. Claude Bernard[18] taught forty years ago that "the blood is an internal medium in which anatomical elements live as do fishes in water." René Quinton[19] showed that our plasma was a fluid which chemically, in so far as the relative proportion of the various elements was concerned, corresponded with sea water. A. B. Macallum[20] also holds that both animal and vegetable protoplasm derive their relations to the elements sodium, potassium, calcium, and magnesium from the composition of sea water which obtained when all forms were unicellular. The labors of Bunge,[21] Jacques Loeb,[22]

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[15] Boeke: Anat. Anz., xx, p. 17, 1902.

[16] Gemelli: Jour. de l'anat. et de la physiol., 42d year, No. 1, 1906.

[17] Willey: "Amphioxus and the Ancestry of Vertebrates," p. 19, 1894.

[18] Claude Bernard: "Leçons sur les propriétés des tissus vivants." pp. 55-58, 1866.

[19] René Quinton: Paris Correspondent, Lancet, April 16, 1904.

[20] Macallum: Trans. Canadian Institute, p. 181, 1903-4.

[21] Bunge: "Physiological and Pathological Chemistry," English translation by Starling, pp. 101, 102, 1902.

[22] Loeb: Pflüger's Archiv, cvii, p. 252, 1905.

Matthews, Fisher, Overton,[23] and others have all contributed testimony to the solidity of this view.

Considered in the light of the anatomical connections of the pituitary with the thyroid and adrenals, and the functions I have ascribed to these organs, the conclusion seems warranted that

In the higher animals, including man, the "test organ" tests the purity of the qualitative homologue of sea water, the blood, for toxic substances and, where possible, causes destruction of these substances.

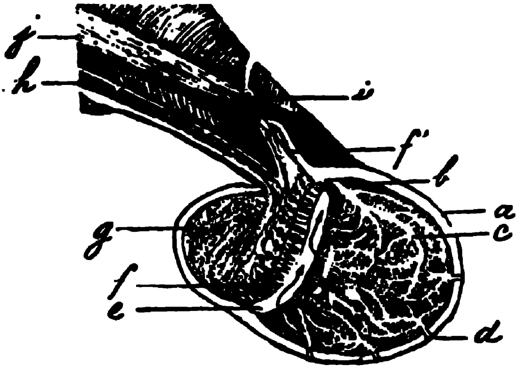

Fig. 1.—Pituitary Body, Containing Immunizing Center (semi-schematic). *a*, anterior lobe; *b*, arteries and, *d*, arterioles; *c*, course of blood diffused through sinusoidal capillaries of epithelium; *e*, cleft into which contents of blood-cells (colloid) and cellular detritus are driven, and whence they pass into lymphatics; *f*, sensory test organ (immunizing center) excited by colloid when the blood (and therefore the colloid) contains certain poisons; *g*, posterior pituitary containing origin of paths to adrenals and thyroid; *h*, tuber cinereum, showing secretory path to adrenals and thyroid; *i*, retro-optic nucleus which transmits, *j*, sympathetic vasoconstrictor nerves to various organs, including the thyroid.

We have only to analyze the pathogenesis of the convulsions that follow removal of the pituitary to realize that the rôle of its test organ is also to prevent general intoxication in the higher animals, including man. This procedure, as observed by Marinesco,[24] Vassale and Sacchi,[25] Masay,[26] and others, produces, as Schäfer[27] expresses it, "muscular twitchings and tremors developing later into spasms." This exemplifies the familiar convulsions caused in children by autointoxication; those ascribed to tetanotoxin; those of puerperal eclampsia which Williamson,[28] Grandin,[29] and others ascribe to poisonous substance circulating in the blood; those provoked in animals by Herter,[30] Krainsky,[31] and in man by Ceni[32] with hypertoxic serum derived from epileptics, a fitting corollary for Pierce Clark's[33] conclusion, based on a study of 150,000 epileptic seizures, that "we must see the pathogenesis in an initial toxin or autointoxication." I have urged in this connection, and others besides myself have found, that in appropriate cases of epilepsy, those in which the thyroid is inadequately active and in which gliosis has not been given time to develop, thyroid extract proves effective in arresting the paroxysms. Need I refer to its corresponding action in the convulsions—of both tetanic and epileptic type—that follow extirpation of the thyroid and parathyroids? Here there is directly introduced into the blood the agent which sensitizes the toxic wastes and renders them vulnerable to the destructive action of the other defensive substances.

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[23] Overton: *Ibid.*, cv, p. 176, 1904.
[24] Marinesco: C. r. de la Soc. de biol., p. 509, 1892.
[25] Vassale and Sacchi: Arch. ital. di biol., xxii, p. 133, 1895.
[26] Masay: *Loc. cit.*
[27] Schäfer: "Textbook of Physiology," i, p. 946, 1898.

THE MODE OF ACTION OF THE IMMUNIZING MECHANISM AND THE GENESIS OF FEVER.—In view of the foregoing facts, physiological, clinical, histological, and zoölogical, the introduction of a toxic into the blood should, by exciting the test organ, awaken the defensive resources of the body to action through the intermediary of the thyroid apparatus and adrenals. Crucial experiments are available to show that such is the case, *i.e.*, that the test organ when excited by a poison stimulates the adrenals and the thyroid apparatus and thus induces destruction of that poison, and, moreover, that when the test organ cannot transmit its impulses to the adrenals and thyroid the autoprotective process does not manifest itself. These experiments were those of Sawadowski[34] and of other investigators referred to below. They indicate, when explained in the light of my views, that

Fever is the physiological expression of the defensive mechanism when a toxic capable of exciting the test organ is present in the blood.

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[28] Williamson: Obstetrics, p. 703, 1903.
[29] Grandin: Grandin and Jarman's "Practical Obstetrics," p. 94, 2d ed., 1900.
[30] Herter: Jour. of Nerv. and Ment. Dis., February, 1899.
[31] Krainsky: Wiener klin. Woch., February 24, 1898.
[32] Ceni: Riv. Sper. di Fren., xxxi, No. 11, 1905.
[33] Clark: Medical News, July 12, 1902.
[34] Sawadowski: Centralbl. f. d. med. Wissch., 26th year, No. 9, p. 161, 1888.

I have urged that the pituitary contained the heat center, and that it produced a rise of temperature through the intermediary of the adrenals and thyroid. The test organ is evidently closely connected with the heat center, for the protective process it awakens when certain poisons occur in the body is a rise of temperature. Now, Sawadowski noted, after injecting putrid substances into the blood, and in accordance with familiar experience, that it caused fever, even *after the cerebrum had been removed* from the midbrain. He found, moreover, that antipyrin controlled this fever. But his experiments revealed an important fact, viz., that section through the optic thalami or the posterior edges of the corpora striata (which, from my viewpoint, also severed the nerve paths from the test organ or heat center to the adrenals and thyroid) prevented these effects. "After these sections," he writes, "neither the putrid materials nor the antipyrin exerted any influence upon the temperature. The sinking of the temperature was not arrested by the putrid substances." The last statement refers to the fact that, notwithstanding the presence of putrid substances which had caused fever, the temperature steadily went down—after the operation—from 38.1° C. in the colon to 31.4° C. This recalls the steady decline that occurs after removal of the pituitary. Ott and Scott[35] also found that the marked rise of temperature that follows the intravenous injection of betatetrahydronaphthylamin in normal rabbits did not occur after they had transected the base of the brain behind the tuber cinereum.

The heat, or thermogenic, center thus influenced cannot be located in the cerebrum, for we have seen that removal of this organ does not affect the temperature. Nor can it be located in the optic thalamus or the corpus striatum, for Ott and Harris[36] provoked the typical rise of temperature by puncturing with a needle, through the mouth, "only the lower surface of the tuber." Its true location is shown by the fact that Ott found a thermogenic center in the anterior portion of the floor of the third ventricle, *i.e.*, immediately above the pituitary. Moreover, it is precisely traversed by the nerves which Andriezen, Gentès,

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[35] Ott and Scott: Jour. of Exper. Med., November, 1907.
[36] Ott and Harris: Therap. Gaz., June 15, 1903.

Joris, and others traced from this organ, and which Andriezen followed to the region of the pons.

Under these conditions, however, transection of the pons should also have prevented the thermogenic action of putrid materials in Sawadowski's experiments. Such proved to be the case. Of this experiment, carried out with the aid of Pawlow, Sawadowski writes: "Following out Ischetschichin's method, a diagonal section was made through the pons Varolii. When the section was complete, free from hæmorrhage or of any condition which might excite the surface of the cut tissues, a gradual diminution of the temperature occurred in the rectum and between the toes. In one experiment, for example, in which the preoperative temperature was 38° C. in the rectum, and 34.5° C. on the skin, nine hours after the operation the first had fallen to 27° and the second to 25° C." This applies as well to the spinal cord; "when the section was made quite high up," he says, "no rise of temperature could be obtained with putrid materials, nor did the antipyrin lower it."

In the portion of the cervical region, however, he found that transection of the spinal cord did not completely prevent the influence of either the putrid materials or the antipyrin. But we have in this paradoxical phenomenon only confirmatory testimony to the presence of a nervous connection between the pituitary and the thyroid apparatus, for in these "low sections," as he terms them, he severed the cord below the origin of the nerves to the thyroid, thus leaving untouched the nerves which connected it with the pituitary and its test organ, though severing the path to the adrenals. What effects were obtained were due to the thyroid apparatus, which remained under the influence of the test organ, and therefore of the thermogenic poison and antipyretic.

These experiments speak for themselves—especially in view of the fact that Sawadowski mentions among the concomitant effects of his sections "disorders of respiration and circulation," and also blueness of the blood—obvious evidences of defective oxygenation. Added to the foregoing evidence, they seem to me to warrant the following general deductions:—

1. Man, in keeping with many animals lower in the phylogenetic scale, is supplied with an autoprotective mechanism.

2. This mechanism includes: 1, the immunizing center, an organ of special sense annexed to the heat center, both centers being located in the pituitary body; 2, the thyroparathyroid glands; 3, the adrenals, and, 4, special nerves which connect the immunizing center (or overactive heat center) with these two sets of organs.

3. The immunizing center, which governs the autoprotective mechanism, is the developed "osphradium" or "test organ" described by zoölogists in mollusks and certain ancestral vertebrates.

4. While the osphradium of primitive animals tests their respiratory fluid, sea water, its prototype, the immunizing center of higher animals, including man, tests the blood, also a respiratory fluid and a qualitative homologue of sea water.

5. When the functional activity of the immunizing center is increased through the presence in the blood of some toxic, i.e., *wastes, toxins or endotoxins, mineral and vegetable poisons, certain venoms, drugs, etc., capable of exciting this center, it stimulates correspondingly the heat center and thus awakens the immunizing process.*

6. Fever indicates that the autoprotective mechanism is active. The rise of temperature is due to the increased production of thyroparathyroid and adrenal secretions, and the resultant increment of metabolic activity. The immunizing process is a consequence of this hypermetabolism, all the immunizing agents, plasmatic and cellular, being produced in greater quantities.

But Lazarus Barlow states we have seen—and he is amply sustained, I may add, by the teachings of clinical experience—that "in pneumonia, erysipelas, cerebrospinal meningitis, typhoid fever, the prognosis is better if the patient's temperature is moderately high than if it is definitely low." This is met by the interpretation of the febrile process I submit in the next conclusion:—

7. Absence of fever in a toxæmia of any kind is due to inability of the immunizing center to react under the influence of the toxic, owing to deficient sensitiveness (inherited or acquired) of this center, or to the fact that the toxic is itself a paralyzant or anæsthetic of its sensory elements.

On the other hand, every practitioner is aware of the dangers of hyperpyrexia. This also finds its normal explanation in the terminal conclusion that:—

8. Excess of fever (above 105° F.) is due to excessive excitation of the immunizing center and a corresponding overproduction of defensive bodies. This condition exposes the red corpuscles and the endothelial cells to proteolytic destruction (hæmolysis and autolysis) along with the pathogenic substances or bacteria.[37]

CONCLUDING REMARKS.—Such are the facts which have led me to believe that the human organism is supplied with an autoprotective mechanism. Its functions, I may add, harmonize with the views of the modern biochemist who has found that increased metabolism is a characteristic of the febrile process; they also coincide with the observations of the bacteriologist that, while most pathogenic bacteria thrive at the normal temperature of the body, they promptly die when it is raised several degrees. They account for the teaching of clinical experience that a higher mortality occurs in apyretic cases than among those in which the febrile process had been active. They explain the harmful influence of hyperpyrexia, since excessive immunizing activity means proteolytic destructions of the blood-cells (hæmolysis) and even of tissue-cells (autolysis) besides the pathogenic agents themselves.

In the practical field, personal experience sustained by that of many colleagues who have carefully studied my doctrines has shown clearly that these embody the lever through which we can overcome infections. We need only analyze the beneficial action of vaccine therapy, of antitoxin, of drugs such as mercury, the iodides, and other so-called "alteratives," to recognize that their tendency, in therapeutic (non-toxic) doses, *is to raise the temperature*—PROOF THAT THE IMMUNIZING PROCESS IS ACTIVE.

Yet, as is well known, the autoprotective resources of the body do not depend only upon the germicidal and autotoxic constituents of the blood-plasma. Indeed, they could not be carried out without the potent co-operation of the phagocytes, the importance of which in immunity has been revealed to us through the genius of Metchnikoff.

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[37] The placing of animals in the heated chamber to determine the influence of high temperatures on the corpuscles is a useless and misleading experiment, since the proteolytic ferment, the active agent in the process, is not increased.—S.

To obtain an idea of the relations of the internal secretions with these defensive cells, we should have at least an idea of their relations with the ductless glands, the manner in which the vital process is sustained in them, and the rôle each type of leucocyte fulfills in this connection. I know of no work in which these features are studied and must, therefore, build up the whole framework of the process, and thus try, at least, to ascertain the nature of the connection between the immunizing process as I have described it in the foregoing pages and the functions of the phagocytes.

THE LEUCOCYTE IN ITS RELATIONS TO NUTRITION, ORGANIC FUNCTIONS, AND IMMUNITY.

Before inquiring into the physiological functions of each of the various varieties of white corpuscles, or leucocytes, it was deemed advisable to study the cell as a unit, and particularly the functional attributes of its main component structures: (1) the nuclear and cellular reticulum or mitoma; (2) the granules.

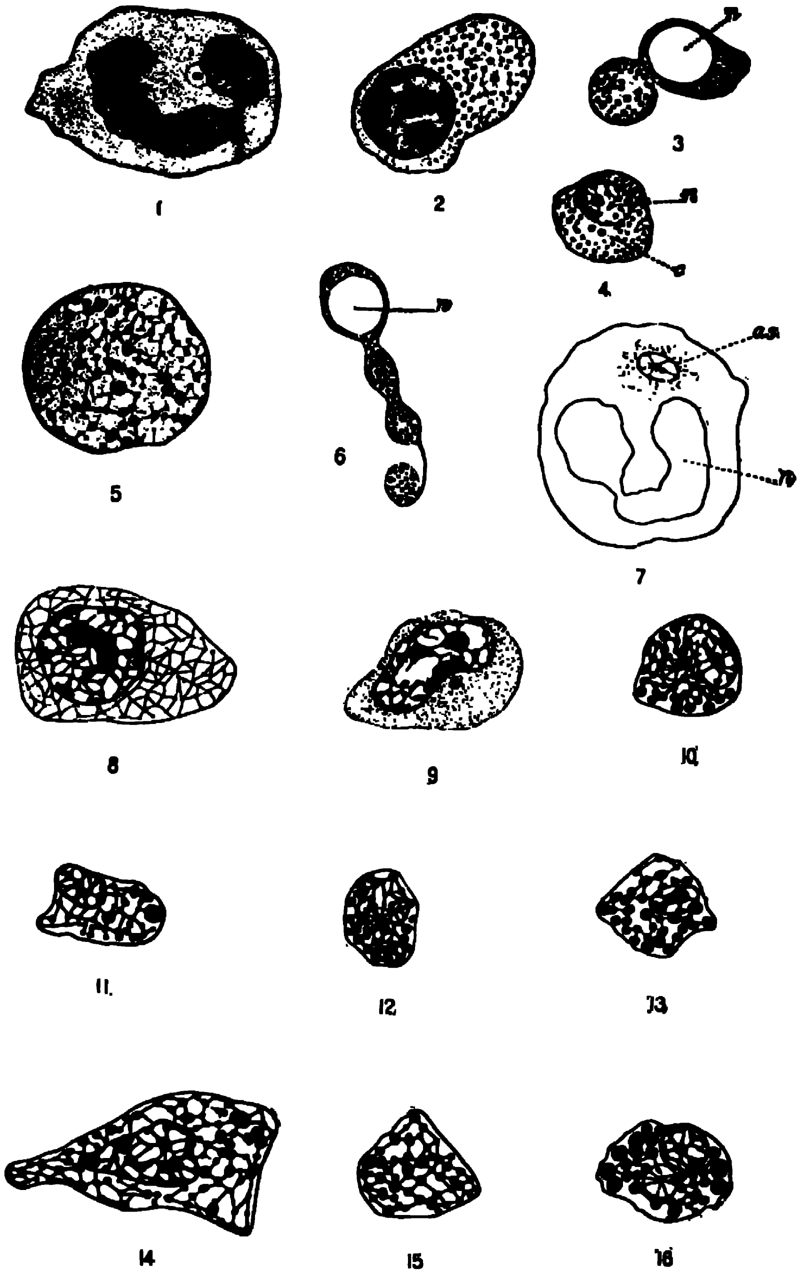
THE MITOMA.—Alluding to basophile leucocytes, Howell[37a] states that the nucleus "is divided into lobes that are either entirely separated or are connected by fine protoplasmic threads." This is well illustrated in the annexed plate from a valuable study of the subject by G. L. Gulland,[38] by Fig. 1, a hyaline leucocyte from a newt's blood. These cells are undeveloped and their protoplasm does not as yet show "threads." But their nucleus is clearly supplied with them even at this early stage—a feature which suggests that the nucleus is an autonomous structure. This is further sustained by the presence, in the perinuclear portion of the cell, of a small body, the astrosphere, shown in Fig. 7, another undeveloped, or "hyaline," cell. This astrosphere is likewise present in fully developed leucocytes, as may be seen in Figs. 10, 12, and 16. Each cell may, therefore, be said to contain two functional centers, each supplied with its net-work of fibers or threads.

[37a] Howell: *Loc. cit.*
[38] G. L. Gulland: Journal of Physiology, vol. xix, 1896.

Heidenhain is stated by Gulland to have found that "the granules are arranged radially to the astrosphere, with the smallest granules next the sphere, the largest at the periphery." This is exemplified with especial clearness in Figs. 10 and 16, and if the threads, or fibers, are traced from the center of the astrosphere, the gradual increase in size of granules as the periphery of the cell is approached is clearly indicated. Heidenhain also concluded, a feature fully confirmed by Gulland, that "there are never any granules within the astrosphere itself." It thus becomes evident that, while the nucleus is an autonomous structure, the same may be said of the astrosphere. In other words, a leucocyte seems to be supplied with two individual, though doubtless correlated, functional systems: (1) the nucleus *per se*, which contains a net-work of fibrils and granules; (2) the astrosphere, which represents the center of the cellular net-work of granule-laden fibrils.

As may be seen in the numerous cells represented in Gulland's plate, which cells have been drawn by him with the utmost care and fidelity to microscopic appearances, the fibers in the nucleus divide the latter into several irregular areas, while the radiating net-work of which the astrosphere is the center forms relatively regular spaces. The fibers in both structures run to their external boundaries, however, precisely as if they were attached to the external limiting membranes of each. And yet the nucleus alone seems to be supplied with such a membrane, while the surface of the cell is not. A prominent feature of these cells is the fact that their protoplasmic exterior is absolutely bare.

After a study of the characteristics of the granules, Gulland writes: "The granules of leucocytes are therefore *not* products of the metabolic activity of the cell imbedded in a structureless protoplasm, as was hitherto supposed, but represent an altered condition of the microsomes [the granules]. They always form part of the cytomitoma [the net-work of fibers] and are therefore *plasmatic*, and not paraplastic. They are probably concerned with amœboid movement, and they and the rest of the mitoma are more visible the more active the cell."



LEUCOCYTES: THEIR MITOMA AND MICROSOMES. *[Gulland.]*

[*Journal of Physiology.*]

Granules, as the plate distinctly shows, are plentiful within the nucleus, and in the cellular substance likewise; in fact, in the latter they are crowded around the centrosphere, the deepest portion of the cell.

If the granules are plasmatic, *i.e.*, formed by substances derived from the plasma, how does the latter reach the minute areas in which the granules are formed? Channels seem to me absolutely necessary for the passage of the blood-plasma, its alkaline phosphates, and other plasmatic salts from which the granules are formed.

The prevailing view that the threads (mitoma) are concerned with the amœboid movements of leucocytes, as also inferred by Gulland, is by no means, it seems to me, incompatible with the possibility of their being plasma-channels, or efferent canaliculi. Indeed, their elasticity does not eliminate the possibility of their being tubular, while their extension and retraction may, as in the sweat-glands, afford the mechanical elements of an expulsive process. "It is certainly interesting to note that, the more active the cells of this series become," writes Gulland, referring to the acidophile (phagocytic) leucocytes, "the more visible become their mitoma and the microsomes which form part of it. The lymphocytes in which no mitoma can be seen are practically non-amœboid. The hyaline cells in which it is not very evident move but sluggishly. The oxyphile cells, with a well-marked mitoma and microsomes, move more rapidly, and the eosinophile cells, whose mitoma and microsomes are the most visible of all, move most rapidly." Again, he says: "It is certain that the length of thread lying between the microsomes varies immensely in different parts of the cell, and the short threads are usually the more deeply stained; so that it looks as though they were *contracted* and therefore *thickened*. On the other hand, the microsomes at the periphery are, generally speaking, the largest, and there can be no doubt that it is the circumference of the cell which moves most and moves farthest." As regards the basophile leucocytes, he states that, "as far as one can judge from fixed specimens, the larger basophile cells seem to have more power of movement than the smaller ones"—a feature easily accounted for, since they are not bactericidal, as are the acidophile leucocytes, It seems probable, however, that in both acidophile and basophile cells the fibers take part in the mechanism through which they travel in the plasma, while contraction, thickening, etc., *i.e.,* the elements of a suction or expulsion process, are present to suggest the identity of the mechanism to which they owe their powers of locomotion.

Basophile leucocytes are not phagocytic; they do not, therefore, ingest foreign substances as do the latter, *i.e.,* by inglobing them. They must, therefore, be provided with a different mechanism for this purpose. If, in accord with my view, the mitoma represents a system of centrifugal canaliculi, it cannot serve for this purpose. Indeed, the external agencies penetrate the cell to the nucleus itself. Thus, W. R. Stokes and A. Wegefarth,[39] alluding to the researches of Bail,[40] say: "After injecting virulent staphylococci into the pleural cavity of rabbits he found that the leucocytes underwent a characteristic change. They formed round, empty bodies, containing several vacuoles in the *nucleus.*"

How did the virulent staphylococci reach the nucleus's vacuoles? Metchnikoff's plate (opposite page 692 in this volume) will assist us in elucidating this question. It not only forcibly illustrates what this distinguished zoölogist sought to show, but likewise, it seems to me, a mechanism of ingestion, differing somewhat from the recognized "ingulfing" or "inglobing" process through which phagocytes take up germs, small particles, etc. An example of this mode of appropriating various plasmatic or foreign substances is illustrated in Fig. 5, which shows bacteria penetrating, from various directions, *into* the cell-wall, while Fig. 16 shows the bacteria *within* the perinuclear vacuole. As all the cells in Metchnikoff's plate are phagocyte, the mechanism of ingestion to which I refer is not only that of basophiles, but is obviously a feature of all leucocytes.

The fact must be emphasized that I say "perinuclear" vacuole, and not "nuclear" vacuole, for, if this and the other germ-laden cells just referred to are carefully examined, it will become evident that the bacteria lie in a pocket contiguous to, but not forming part of, the nucleus itself. I would not say, therefore, with Bail, "vacuoles *in* the nucleus," but vacuoles *around* the nucleus. Indeed, Gulland refers to Heidenhain as considering that "the nucleus lies free in the interfilar spaces, and is not organically connected with the cell-substance." This is quite in accord with my view, and it seems to me that it represents the cavity into which bodies ingested by leucocytes normally arrive, though smaller vacuoles are likewise present in the cytoplasm.

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[39] W. R. Stokes and A. Wegefarth: Bulletin of Johns Hopkins Hospital, Dec., 1897.

[40] Bail: Berliner klin. Wochenschrift, Oct. 11, 1897.

The actual presence of this perinuclear vacuole from which canaliculi would start appears to me indicated in several of the figures in the annexed Gulland's plate. Fig. 8, for instance, stained with iron-hæmatoxylin, shows that the nucleus is surrounded by an irregular limiting material of some kind; but if we compare the outline of this limiting substance with that of all the succeeding cells, an interesting feature asserts itself, viz.: its thickness is extremely variable. Although 12 may be said to be moderately regular, the others, in the following sequence: 11, 10, 13, 8, 9, and 14, are increasingly irregular. If, now, this irregularity itself is scrutinized, a significant fact is revealed: *i.e.*, the bulges, or projections, in the limiting structure are all at the expense of the nucleus. In Fig. 9, for instance, just above a clover-like figure near the center of the cell (probably the astrosphere), the marked bulging shows every evidence of having been formed by a substance which had compressed the nuclear substance inwardly. The stages of this compression are exemplified in Metchnikoff's plate, by Figs. 16 and 15, successively. In the former a single mass of liquid and germs is seen to have indented the center of the nucleus on one side, while in the second figure three cavities are shown which have distorted it. (The nucleus is indicated by an *n*.) In *both*, however, the compression has exceeded the normal boundaries of the limiting structure, and centrifugal bulging has occurred at the expense of the perinuclear protoplasm or cytoplasm. So marked has this become in Fig. 14 that the nucleus is not discernible.

The identity of the mitoma as a system of canaliculi suggests itself in another way. I have shown that the axis-cylinders of nerves, neuroglia fibrils, etc., contained blood-plasma. Such being the case, if the fibers or "threads" in leucocytes are likewise plasma channels, they must stain, as do the former, when treated to various dyes. We have seen (pages 541 to 543) that methylene-blue dissolved in salt solution and injected into the vessels of a living animal colored the axis-cylinders blue, according to Ehrlich, and that this investigator defined the conditions of nerve-structure essential to the methylene-blue reaction as "oxygen saturation and alkalinity"—the very attributes of blood-plasma. Referring to the various stains used by him, Gulland says: "In examining the basophile cells I used almost entirely various methylene-blue solutions," and, later on: "The basophile cells of the dog's intestinal villi, when fixed with absolute alcohol and stained with alcoholic methylene-blue, give exactly the same results, as to mitoma and granules, as other basophiles." Evidently, as regards the methylene-blue stain, nerve-fibrils and mitoma (my canaliculi) are similar. Again, besides the plate reproduced here, Gulland presents two colored plates, in which the characteristic affinity of each cell for stains appears; the six basophile leucocytes stained with methylene-blue (normal) distinctly show that structures which stain most deeply are the chromatic, *i.e.*, the nuclear mitoma; then, more faintly, the cellular mitoma. It seems clear that, as regards methylene-blue stain at least, the conditions are similar to those of nerves as far as the mitoma—or canaliculi—are concerned.

The same correspondence exists between nerve-fibrils and the mitoma when hæmatoxylin is used. We have seen (page 536) that, according to McCarthy, the rods that project radially from the axis-cylinder "stain with carmine and hæmatoxylin, which do not stain the myelin." The fact that the axis-cylinder takes hæmatoxylin hardly needs to be emphasized, its use in histological laboratories when nervous structures are studied being second only to picrocarmine for general staining. A beautiful example of hæmatoxylin-stained human cerebrospinal and sciatic nerves is to be found in Clarkson's "Histology," page 204, for instance. All the eosinophile leucocytes shown in the annexed plate, in which the nuclear and the perinuclear granules and mitoma are so clearly defined, were stained with Heidenhain's iron-hæmatoxylin, which only differs from the usual solution in that it colors the cellular elements that take it a dark gray or black. This also shows that it is not only with the mitoma of basophile leucocytes that the staining characteristics of nerve-fibrils—*i.e.*, plasma-containing channels—coincide, but also with that of eosinophile cells. Even Apáthy's fibrils are recalled by the effects of corresponding stains, for Senn writes,[41] referring to the minute anatomy of the leucocyte: "The reticulated structure is well shown by staining with chloride of gold, which stains the protoplasmic *strings*, but not the interstitial substance." It seems quite evident, therefore, that *the mitoma,* i.e., *the intracellular and intranuclear networks of fibers in mature leucocytes, are canaliculi for blood-plasma.*

FUNCTIONAL MECHANISM OF THE LEUCOCYTE.—I have expressed the view that the nuclear canaliculi open into a vacuole which surrounds the nucleus (see Fig. 14 in Gulland's plate) and that the outer wall of this vacuole acts as terminal for some of the canaliculi of the cell-substance. Although, as suggested by Fig. 11, the canalicular orifices that open into the vacuole from both directions may correspond (the nuclear orifices being in that case opposite the cellular openings), such is by no means always the case. Indeed, in Fig. 16, for example, but two or three of the external canaliculi seem to be connected with the vacuole, while this cavity serves as terminal for all the *intra*nuclear channels—if such they are.

Is the connection between this vacuole and the exterior of the cell direct or indirect: *i.e.*, through separate channels leading directly to the exterior or to those connected with the astrosphere's system? That the communication is independent of the latter is emphasized by the presence of granules in the path of all canaliculi, as shown in Gulland's plate. A continuous function depending upon an inflow of plasma would obviously be in constant danger of arrest were the granular channels centripetal pathways. Again, in all leucocytes, acidophiles as well as basophiles, the nucleus stains in the same manner, the granules alone, as we have seen, showing variations in this particular. The same may be said of the reticulum, for we have seen, by the staining reactions, that the compounds composing the granules are bathed in oxidizing substance, i adrenoxidase. This uniformity of nuclear and cellular fluids in the canaliculi suggests the presence of a very common mechanism—one, indeed, which must serve to *eliminate* its contents, judging from the fact already mentioned, that the intracellular granules increase in size outwardly, the largest granules being at or near the surface. A common centrifugal canalicular system again suggests the presence of a system common to all leucocytes, whether phagocytic or not, for the introduction (not necessarily of particles or other discernible agencies) of more or less liquid or viscid bodies required by the cell for its own nutrition, or connected with its own physiological functions: *i.e.*, the elaboration of granules. The canaliculi serving only for the centrifugal elimination of the latter, the centripetal paths must penetrate to the vacuoles *between* the canaliculi, or "threads," as already explained, and as shown in Metchnikoff's plate, Fig. 5. We are evidently not dealing here with mere inclusion or pseudopodial flowing around the germs, for the latter may be seen to penetrate the cell between the granules, and, judging from Figs. 13, 14, 15, and 16, directly into the perinuclear vacuole itself.

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[41] Senn: "Principles of Surgery," 3d ed., 1901.

Is the cell supplied with *centripetal* canaliculi *in addition* to the centrifugal system which I believe to be represented by the reticulum? The fact that micro-organisms can penetrate directly *into* the vacuole between the external layer of granules is not alone to suggest that such is the case, but the manner in which the leucocyte takes up stains likewise does so. As can readily be seen, the absorption of the dye by the cell occurs without involving any alteration of its shape which can at all be associated with the process. That the absorption cannot occur through the visible canaliculi: *i.e.*, those that take stain because they constantly contain fluid, is rendered very probable by the presence of the granules, which must entirely close their external orifices. It must occur, therefore, through paths presenting some analogy to the pores of certain sponges, which allow the surrounding water to pass into the interior of the sponge, so long as it does not carry any harmful products along with it (Metchnikoff). And yet the fact that such a system of channels does not exist is shown by the promiscuous directions taken by bacteria in penetrating into the cell. Indeed, their bodies are not directed axially toward the perinuclear vacuole; they seem, once within the external layer of granules, to point in almost any direction. We are brought back, therefore, to the soft, yielding, protoplasmic cell-substance of the amœba, which will allow liquids to transude easily through it, and the more dense materials to cleave their path into it and down to the vacuole, without leaving a wound behind them. "On introducing pigeon leucocytes filled with anthrax bacilli (to which the pigeon is very refractory) into bouillon," says Metchnikoff, "bacilli grow, *pierce* the protoplasm of the cells, and form well-developed filaments, showing definitely that the bacilli were inglobed in a living condition." We might say "ingest," however, for the perinuclear vacuole asserts its identity as a digestive organ—the familiar digestive vacuole—in several ways: *i.e.*, as a cavity in which all the materials that supply the cell with functional energy—*i.e.*, with life—are drawn.

Metchnikoff,[42] referring to the intracellular digestion to which amœbæ submit the materials they ingulf, writes as follows: "A closer observation of the group of protozoa compels us to the conviction that this digestive function must play an important rôle in the mutual relations of these lowly organisms. Many rhizopoda and infusoria live in media swarming with other unicellular organisms, including bacteria. The latter, which multiply very rapidly, serve as food to many of the protozoa. Thus, various amœbæ devour bacilli, which undergo certain definite changes in the interior of the protoplasm. Without altering their shape, the bacilli acquire the power of taking up solutions of vesuvin, which does not stain these microbes when living in their natural conditions. Since precisely similar changes are also observed in the interior of vorticellæ and infusoria, which live on bacteria, it is evident that they are due to a digestive influence exerted by the contents of the protozoa." This conclusion is in harmony with the observation of B. Hofer[43] on digestion in amœbæ. This investigator has shown that "the more the food is altered in the interior of these rhizopods, the more easily does it stain with aniline dyes." When we consider that aniline dyes include methylene-blue, we have evidence, in view of Ehrlich's observation, that the "conditions essential to the methylene-blue reaction" are "oxygen saturation and alkalinity," that the prototype of amœba, the leucocyte, must owe its nuclear functional activity to the plasma as exogenous reagent.

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[42] Metchnikoff: "Lectures on the Comparative Pathology of Inflammation," translated by F. A. and E. H. Starling, pp. 18 *et seq.*, 1891.

[43] B. Hofer: Jenaische Zeitschrift, vol. xxiv, 1889.

Metchnikoff further says: "We may often see flagellated monads taking up filaments of leptothrix several times as long as themselves, and finally inclose them in their digestive vacuoles." The process of ingestion is beautifully shown in the plate opposite page 692, in Figs. 19 and 20, the organisms here being spirilla of Asiatic cholera. "It is sometimes possible to follow all the changes undergone by the bacteria within an infusorium," continues the same investigator, "as in the case of the digestion by stentor of the sulphobacterium thiocystis, observed by le Dantec."[44] . . . "It is evident that the digestive function of the protoplasm of the protozoa must hinder the invasion of these animals by the lower organisms, and it is only in certain special cases that the latter can live as parasites within the rhizopoda and infusoria."

The true identity of the perinuclear vacuole seems further emphasized by the following lines, also quoted from Metchnikoff's text, that is to say, as interpreted by his translators: "The sponges are of such undifferentiated organization that they were long considered to be colonies of protozoa, consisting, like the protospongia, of separate flagellated and amœboid individuals. Later on, it was, however, ascertained that they bore a certain relationship to the polypi and their allies (cœlenterata)." . . . "There are a few species, such as the siphonochalina coriacea, whose mesodermic cells alone inclose all foreign bodies, so that the cylindrical cells of the endoderm merely serve to keep up the continuous passage of the fluid through the sponge. The *phagocytes* of both layers have the power of rejecting insoluble matters, which collect in the larger efferent canals." . . . "We are, however, chiefly concerned here with the fact that the mesodermic phagocytes are able to *digest* the substances as well as to inglobe them, and to *reject* the insoluble residue."

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[44] Le Dantec: "Recherches sur la digestion intracellulaire," Lille, 1891.

The nature of the digestive process has, however, remained obscure. "The bacilli which have been inglobed by leucocytes," continues Metchnikoff, "are much more rapidly digested in the case of mammals that are either naturally refractory, as the dog and fowl, or have been rendered artificially immune against anthrax by vaccination, as the rabbit. This fact is shown by the researches of Hess, as well as my own. It is easy to follow the digestion of many other microbes within the leucocytes. Vacuoles are often seen to form around the bacteria that have been swallowed, just as we have noticed in the digestion of nutrient material by the protoplasm of the protozoa and the myxomycetes. I have been able to observe the changes undergone by the spirilla of recurrent fever in the leucocytes of monkeys, as well as those undergone by the vibrio septicæmiæ in the leucocytes of immunized guinea-pigs, and those by erysipelas streptococci in the leucocytes of man, etc. We are at present ignorant of the precise manner in which this digestive and destructive action is accomplished, and do not even know whether the substance which kills the microbes is a ferment or not."

Before submitting this question to analysis the manner in which the products of digestion, both the nutritional elements and the excrementitious products, are disposed of must be ascertained.

In the sponge the materials rejected by the phagocytes "and which collect in the larger efferent canals," says Metchnikoff, are eliminated "through large apertures of crater-like shape, the walls of which, according to some authors, are furnished with muscular fibers." What have we in the leucocytes to fulfill this function: *i.e.*, to represent what in the higher forms constitutes the intestinal canal? This appears to me particularly well shown in several of the figures in Gulland's illustration. In Fig. 10, for instance, a few "fibers" —our canaliculi—may be seen to project from the inner aspect of the line which to me represents the practically empty side of the vacuole. The same arrangement is clearly to be seen in Figs. 11, 12, 13, and 16.

If all the foregoing features are considered collectively, they suggest that:—

1. *Leucocytes can ingest solid, semisolid, and liquid bodies through their cell-substance in two ways: (1) by projecting pseudopodia which infold or inglobe them; (2) by absorbing them without projecting pseudopodia.*

2. *Solids and semisolids are mainly ingested by infolding, and semisolids and liquids by absorption; but all substances, with what plasma accompanies them, are collected in a vacuole that surrounds the nucleus and in which the latter lies free; and, at times, in the smaller vacuoles in the cytoplasm.*

3. *What physiologically useful bodies are formed in the cell are mainly elaborated in the nuclear canaliculi and the perinuclear vacuole, and are collected in the form of granules in the canaliculi.*

4. *All the functions of the cell are probably governed by the astrosphere.*

THE GRANULES AS SECRETORY PRODUCTS.—Gulland refers to granules or microsomes in the following words: "Ehrlich regarded the seven varieties of granules which he described as being all formed by the cells, and as being either reserve material or products for excretion. Hankin [1892-93] took the view that the acidophile granules were secretory products, containing 'alexins,' and destined to be secreted into the blood or lymph. Kanthack, Hardy, and Keng have taken much the same view of these special granules. Sherrington has thrown doubt upon it, and Metchnikoff disputes it and regards the eosinophile granules as reserve material." As viewed from my standpoint, the granules simultaneously represent reserve material *and* products of excretion. These processes are not the only ones, however, with which leucocytes are concerned.

Bail, to whose investigations I have already referred, is also stated by Stokes and Wegefarth[45] to have observed that, after the vacuole "in the nucleus" had formed, "the granules generally disappeared." Furthermore, he noted that upon destroying the staphylococci by adding ether, and diluting the centrifugalized sediment, the granules showed a dancing motion, and were seen to *leave the periphery of the cell* and enter the surrounding medium. Evidently at least *some* of the granules must have been dropped or ejected by the leucocytes, and their canaliculi thus freed of the impediment their presence constituted.

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[45] Stokes and Wegefarth: *Loc. cit.*

This is sustained by a closer examination of the question,—the purpose of Stokes and Wegefarth's paper, who used in their researches blood taken from about five hundred persons. The granules, when observed by them with the aid of artificial light, "resembled those of the eosinophilic or neutrophilic leucocyte." Kept at the temperature of the room, the latter showed no activity, but exposure for an hour to a temperature of 35° C. caused them to become active. The following lines are quoted from their article: "At times the granular leucocytes become actively amœboid, and the granules *within* the neutrophile exhibit a characteristic activity which might be compared to the swarming of bees around a hive. The number of fine granules free in the plasma is perceptibly increased. The eosinophilic granulations also show a less vigorous tremulous motion, and both varieties follow the changes in the direction of the pseudopodia, the protoplasm being thrown out first, and the granules following. The characteristic dancing motion of the granules in the neutrophilic leucocyte can be brought out very plainly by simply mixing the drop of blood with an equal amount of distilled water containing 1 per cent. of alcohol. The granules become very active and present a characteristic picture." . . .

"Can these granules be actually seen to leave the leucocyte? It is certainly not easy to be sure, even after continuous observation for an hour or more, that one has actually seen one of these granules leave an amœboid leucocyte. We think, however, that we have observed this phenomenon upon several occasions, both in fresh specimens of blood exposed to 35° C. and in blood to which 1 per cent. of alcohol has been added." Farther on in their text they say: "Many fine granules can be seen in the clear plasma and around the neutrophile, and it would seem that occasionally a granule leaves the active leucocyte and becomes free in the surrounding fluid."

Bail's observation, however, that the granules actually leave the periphery of the cell has been sustained by other observers. Gulland refers to this feature of the problem in the following words: "It has often been remarked that the large cells show a great tendency to leave their granules behind them; thus, one might come on a group of granules while the nearest cell was far away. Ballowitz was, I think, the first to declare that all or most of these groups of granules were attached to the cell by fine protoplasmic bridges. It is not always easy to show this." Gulland then says, referring to a figure in one of his plates (not shown in that reproduced herein), in which the granules are evidently disunited from the cell: "In the cell shown in Fig. 31, which was so isolated that there could be no doubt that all the granules represented belonged to it, no trace could be made out of threads extending from granule to granule. They are probably stretched too much to allow them to be visible."

The absolute separation of the granules from the cell witnessed by Bail finds its complementary confirmation in the observation of E. B. Sangree,[46] who, after patient watching,—sometimes several hours at a time,—states that he saw "three granules escape from an eosinophile cell, and wander away until lost under rouleaux of red corpuscles, after having reached a distance of some six diameters from the parent-cell." . . . . "While inside the cell," says this pathologist, "these granules had participated in the constant, though rather sedate, movements of the granule mass,—but owing, doubtless, to the difference in specific gravity of the containing medium,—instantly upon emerging from the parent-cell they underwent the wildest possible gyrations. The first to come out were two attached pole to pole, and these rolled frantically over each other, pushed this way and pulled that, all the time oscillating widely and rapidly, yet constantly and definitely traveling farther and farther from the cell, until finally lost to view. The single granule behaved in an exactly similar way. I noticed, too, that before becoming lost to view the motion of these granules had become considerably less marked and approximated more that ordinarily seen in these bodies." If these facts are considered as a normal sequence to the evidence adduced that the cellular net-work of fibers represents the secretory system of the leucocyte, it seems permissible to conclude that:—

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[46] E. B. Sangree: Philadelphia Medical Journal, March 12, 1898.

The granules in leucocytes are the products of an intracellular metabolic process and represent a true secretion.

THE PHYSIOLOGICAL CHEMISTRY OF LEUCOCYTES.—A feature which clearly points to the autonomy of the nucleus and of the net-work of canaliculi in all leucocytes is the uniformity with which they all stain with similar dyes. The nuclear canaliculi and granules and the canaliculi of the cell-substance all take the aniline dyes, methylene-blue and methyl-green, for example: evidence that in *all* leucocytes the structures mentioned must find in the adrenoxidase a source of energy as do other organs.

Beginning with the nucleus, with what chemical body contained in this part of the cell could the adrenoxidase initiate and sustain a reaction? It is, of course, not the composition of the nuclear *granules* that this question involves, but that of what might be termed the nuclear ground-substance. Foster refers to this substance in the following words: "There is present, in somewhat considerable quantity, a substance of a peculiar nature, which, since it is confined to the nuclei of the corpuscles, and further seems to be present in all nuclei, has been called *nuclein.* This nuclein, which, though a complex nitrogenous body, is very different in composition and nature from proteids, is remarkable, on the one hand, for being a very stable, inert body, and, on the other, for containing a large quantity (according to some observers, *nearly 10 per cent.*) of *phosphorus,* which appears to enter more closely into the structure of the molecule than it does in the case of proteids." We evidently have, in the nuclein of the nuclear ground-substance, a body which, as does lecithin in the myelin of nerves, myosinogen in muscles, etc., enters into active combination with the oxidizing substance, *i.e.,* adrenoxidase, and the resulting reaction must necessarily yield functional energy, as elsewhere in the organism.

The character of the reaction which the simultaneous presence of nuclein and the oxidizing substance within the precincts of the nucleus sustain is clearly suggested by the kind of dyes taken by the canaliculi (both of the nucleus and of the cell-substance) and the perinuclear vacuole. E. T. Williams,[47] in a study of the chemical properties of leucocytes, refers to this feature of the problem in the following words: "The nuclei of all three classes stain best with alkaline dyes, as methylene-blue, methyl-green, or dahlia. They are, therefore, acid." Farther on, he says: "We have seen that all nuclei are acid. They owe this property, without doubt, to the nuclein which they contain. Nuclein is acid. When boiled *with alkalies* it yields phosphoric acid. Phosphoric acid, it may be remarked, is the only mineral acid which does not coagulate albumin. It is the presence of this acid undoubtedly which makes nucleïn acid. According to the experiments of Kossel, quoted by Vaughan and Novy,[48] nuclein, when boiled with acids, yields certain organic, albuminoid bases, as adenin, sarcin, xanthin, spermin, and others." . . . "We must conceive, therefore, of nuclein as some sort of a phospho-albumin whose composition has not been precisely determined." The source of the various chemical bodies involved in these processes is shown in the following lines of Professor Foster's: "The ash of the white corpuscles is characterized by containing a relatively large quantity of potassium and of phosphates, and by being relatively poor in chlorides and in sodium. But, in this respect, the corpuscle is merely an example of what seems to be a general rule (to which, however, there may be exceptions), that, while the elements of the tissues themselves are rich in potassium and phosphates, the blood-plasma on which they live abounds in chlorides and sodium salts."

The chemical process involved may easily be traced with the foregoing factors as main elements: The blood-plasma (if the views already submitted are sound) evidently reaches the nucleus through the intercanalicular substance of the cell-body; this is shown by the fact that this substance likewise—though to a less marked degree—stains with methylene-blue. Under ordinary circumstances, according to microscopical evidence, the perinuclear vacuole is practically collapsed: *i.e.*, its nuclear wall is more or less close to that of the cell-body. This is well shown in Gulland's plate, by Figs. 10 and 12. The nucleus thus bathes in blood-plasma, and its canaliculi become filled with the latter along with the vacuole. The nuclein of the nucleus under these circumstances itself bathes in the plasma, being thus exposed to the action of the latter's oxidizing substance or adrenoxidase.

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[47] E. T. Williams: Boston Medical and Surgical Journal, Sept. 5, 1901.
[48] Vaughan and Novy: "Ptomaines and Leucomaines," 1891.

Still, this suggests the presence of a stream of plasma flowing through the nucleus itself, with the canaliculi as emunctories. The contraction and retraction of the canaliculi—or reticulum—to which Gulland and others refer represent the only mechanical device in the cell by means of which the vacuole can be drained.

These minute vessels probably serve as continuous channels for the stream of plasma, which contains, besides the adrenoxidase, the alkaline salts necessary to the intracellular process. The plasma's adrenoxidase and the nuclein's phosphorus, thus brought into contact, liberate considerable heat, and the alkaline salts in the plasma then take part in the reaction to which Williams refers, and which involves, we have seen, the formation of phosphoric acid and other agencies to which I will presently allude.

We must not lose sight of the fact, however, that nuclein is derived from nucleo-proteids, and that during the oxidation process waste-products are formed: we have in the "adenin, sarcin, xanthin, spermin," etc., to which Williams refers, a series of catabolic products. This awakens an important pathological feature. We have seen that, when nucleo-proteids undergo cleavage in the organism, the process involved must be brought to a finish: *i.e.*, to the stage of phosphoric acid formation. The penalty, if completion does not attend the series of reactions, is the presence in the blood-stream of the above-mentioned purin bases, which are now considered, we have seen, as the source of the so-called "gouty diathesis." Slight insufficiency of the adrenal system, therefore, by reducing the adrenoxidase and thyroiodase in the blood, must inhibit the intracellular reactions that I have just outlined, thus giving rise to this disorder. Or the injudicious use of rich foods, by surcharging the proportion of nucleo-proteids taken up by the cells, may lead to the same result though the normal proportion of adrenoxidase and thyroiodase—the latter, we have seen, playing an important rôle by sensitizing the phosphorus to oxidation —be present in the plasma.

Another phenomenon which appears to me elucidated by the presence of the adrenoxidase of the plasma is the manner in which worn-out leucocytes are destroyed. As frequently observed by histologists, each of the varieties may be seen at a given time to become "oxyphile," or oxygen-loving, and to undergo disintegration, a preparatory step to proteolysis here. Even the eosinophile leucocytes, which, according to Metchnikoff,[49] are unable "to inglobe foreign bodies, and therefore cannot act as phagocytes," are destroyed by proteolysis. The affinity of these cells for acid dyes might account for their oxidation, however, and suggest a limit; but such a limit does not exist, for basophile cells also yield to the same agency. Indeed, Gulland, referring to a figure in his colored plate which gives a vivid illustration of a cell undergoing disintegration, describes it as follows: "Degenerated basophile cell from the mesentery of newt. Methylene-blue." In other words, an eosinophile is always acidophile, while a basophile is only acidophile when it is dead or about to die. We have seen that methylene-blue stains oxygen-laden media; hence, the adrenoxidase is evidently an active factor (as amboceptor) in the destructive process.

It seems to me that we can conclude from the above data regarding the physiological chemistry of leucocytes, or white blood-corpuscles, that:—

1. *The granules which constitute the secretion of all varieties of leucocytes are the products of a continuous reaction in the nucleus, in which the nuclein of its nucleus, the materials ingested by the cell, and the plasmatic adrenoxidase, thyroiodase, and alkaline salts take part.*

2. *When a leucocyte becomes functionally incompetent it is destroyed by proteolysis in the blood-plasma.*

CLASSIFICATION OF LEUCOCYTES.—I have proceeded as far as I could with our analysis of the leucocytes as a unit, and it now becomes necessary to ascertain, if possible, the functions of the various types which histologists, headed by Ehrlich, have established with the aid of staining methods.

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[49] Metchnikoff: *Loc. cit.*, p. 115.

Kanthack and Hardy[50] not only give a clear, though succinct, outline of the various varieties of cells, but they emphasize features of the problem which are of special interest to us. After briefly reviewing the more prominent contributions to our knowledge of the subject since Wharton Jones's memoirs, published in 1846, including the investigations of Rindfleisch (1863) and Max Schultze (1865), they write as follows:—

"After Max Schultze, no further advance was made or, indeed, was possible in the histological analysis of the sporadic mesoblast, until Ehrlich, in 1878, furnished a rational basis for the use of staining reagents by his far-reaching discovery that the elective affinity of certain constituents of tissues for particular stains could be referred to two factors: the *chemical* nature of the staining substance employed and—a point too often neglected by workers who have followed his methods—the nature of the medium in which the stain is dissolved.[51] Ehrlich drew particular attention to the granules, the possession of which characterizes various forms of wandering cells. These he divided into five classes, differing either in their special affinity for bases, acid, or neutral dyes, or in size. The α or eosinophile granulation colors *only* with acid dyes; the β granulation colors with both acid and basic dyes (amphophile); the γ granulation colors *only* with basic dyes, and the individual granules are large; the δ granulation colors *only* with basic dyes, but the individual granules are small; and the ε granulation colors *only* in neutral dyes.

"The nomenclature of the granules was extended to the cells bearing them. Thus, the various forms of white cells found by Ehrlich in blood were: I. A small cell free from granules, to which the name lymphocyte was given, from the fact that it appears to be developed in lymphoid tissue. This is the small, non-amœboid form of Max Schultze. II. A cell characterized by possessing fine granules and one or several nuclei. This is by far the most numerous form of white blood-corpuscles in mammalia, and was found by Ehrlich to be neutrophile in man, and amphophile in rabbits and guinea-pigs.

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[50] Kanthack and Hardy: *Loc. cit.*, p. 82.
[51] All the italics are my own.

III. The eosinophile cell, or coarsely granular cell of Wharton Jones and Max Schultze. It occurs only in small numbers in the blood of mammalia, but is abundant in the blood of lower vertebrates. IV. A basophile cell with fine basophile granules (δ granulation).

"The mononuclear amœboid cells of Max Schultze are apparently grouped with the neutrophile cells by Ehrlich. In addition to these forms Ehrlich describes a basophile cell with coarse granules (γ granulation), occurring mainly in connective tissues and also in the blood of frogs, but not in the blood of mammals. These he calls 'Mastzellen.' . . .

"From what we have said so far it will be seen that the group of finely granular blood-corpuscles described by Max Schultze includes the amphophile and neutrophile and the finely granular basophile cells of Ehrlich. Since Ehrlich's work no contribution to our knowledge of the morphology of the wandering cells has been made except on points of detail. Mention must, however, be made of the group of cells recognized by Metchnikoff[92] in his treatise on inflammation. The term 'leucocyte,' originally applied by the French school of physiologists, is used to designate wandering cells, and the following varieties are recognized: (I) lymphocytes; (II) mononuclear leucocytes with abundant protoplasm and a round nucleus; (III) polynuclear leucocytes, or 'leucocytes neutrophiles'; (IV) eosinophile leucocytes."

My purpose being to ascertain the physiological functions of the various types, Ehrlich's four classes, by affording definite microchemical limits, will probably prove more useful than the simplified groupings that other histologists have introduced, and which, by reducing the number of divisions, have tended to efface landmarks that can serve as clues for research. I will preserve, therefore, Ehrlich's classification, and try to ascertain whether the various types of cell do not differ physiologically from one another as they do histologically.

Lymphocytes and Hyaline Cells.—The first cell of the Ehrlich series, the lymphocyte, seems fully entitled to the position accorded it by histologists in general: that of a leucocyte in process of development. The cellular substance is devoid of canaliculi (or mitoma) and of granules, although the nucleus itself is supplied with both, and is evidently functionally active. Lymphocytes are considerably smaller (6 to 6.5 μ) than leucocytes, and represents less than one-fourth of the total number of these cells. They are devoid of amœboid motion. Hyaline cells have been classed in the same category, the cell-body being likewise free from granules, as shown in Gulland's plate, Fig. 1. Both may become active, however, before complete maturity is reached.

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[92] Metchnikoff: *Loc. cit.*

NEUTROPHILE LEUCOCYTES.—These are extremely important members of the leucocyte family, for they represent fully three-fourths of the white cells of the blood, and constitute Metchnikoff's main group of phagocytes. They are termed "neutrophile" by Ehrlich because their granulations stain with both acid and basic dyes. Their reaction to acid dyes is very much less intense, however, than is the case with purely acidophile cells, according to Kanthack and Hardy. Their granules are small as compared to those of other acidophiles. Though termed "polynuclear" leucocytes by Metchnikoff, the masses thought to represent as many nuclei are united by thin bridges, thus constituting a single nucleus. Especially is this likely, since the only other type of cell deemed phagocytic by Metchnikoff is a mononuclear cell. Gulland contends that no shape of nucleus is invariably associated with granules of a special kind. It seems evident, therefore, that the phagocytic cells are only distinguishable by their affinity for alkaline dyes and a slight affinity for acid dyes, and by the concurrence of these histological properties with small granules.

Kanthack and Hardy, who refer to this leucocyte as a "finely granular oxyphile cell," speak of it as follows: "It has a very limited and precise distribution, for, under normal conditions, it is entirely absent from extravascular spaces, and occurs *only in the blood*,[53] where it is by far the most numerous corpuscle, forming 20 to 70 per cent. of the total number of white corpuscles. The fluctuation in this percentage is probably due, in the main, to the great periodic variations in the number of lymphocytes present in the blood. Thus, the effect of a meal is to cause a considerable increase in the number of lymphocytes in the blood, and, therefore, a fall in the share of the total white corpuscles due to finely granular cells. If this disturbing factor be eliminated," continue these investigators, "and the percentage of the finely granular oxyphile cells be taken of the adult white corpuscle only, this is found to be always very high: in man, 75 to 90 per cent."

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[53] All italics are my own.

Metchnikoff, referring to the phagocytic properties of these cells, writes as follows[54]: "Even outside the organism these amœboid cells readily inglobe a large number of foreign particles with which they may come in contact, and they may often be seen literally crammed with all sorts of granules. Like the amœbæ, they swallow not only inert bodies, such as granules of carmine or other substances that are insoluble in the fluid surrounding the leucocytes, but also a large number of living organisms." This is merely quoted to emphasize the fact that the leucocytes differentiated by Ehrlich from all others by the term "neutrophile" are, irrespective of the form of their nucleus, the wandering cells which Metchnikoff has shown to fulfill the physiological function he has termed "phagocytosis."

THE NEUTROPHILE LEUCOCYTES IN ASSIMILATION.—The property which these cells so strikingly show: *i.e.*, their ability to ingulf or rather ingest substances of all kinds, seems to me to suggest that they are intrusted with another rôle in the body: *i.e.*, *its nutrition.* Macallum[55] observed, in sections of intestines taken from animals first starved, then fed upon a substance containing albuminate of iron, free leucocytes crowded with granules of iron-pigments in the intestine. Some of these cells appeared to pass out through the epithelial cells, while others advanced into the subepithelial elements. Macallum also found them in the venules of the villi, the spleen, etc.

We have just seen the reference of Kanthack and Hardy to the "considerable increase in the number of lymphocytes in the blood, and, therefore, a fall in the share of the total white corpuscles" caused by a meal. Both these two phenomena become normal events instead of a "disturbing factor" if the process of digestion includes the use of a large proportion of adult or fully developed leucocytes to transport various materials from the intestinal canal to various parts of the organism. It is evident that under these circumstances the immediate neoformation of lymphocytes, and their rapid growth, as is probably their wont, to the state of mature cells, becomes a *sine qua non* of continued existence.

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[54] Metchnikoff: *Loc. cit.*, p. 115.
[55] A. B. Macallum: Journal of Physiology, vol. xvi, 1894.

Overlooking the possibility of such a function, and led by his own hypothesis to ascribe to intracellular processes the presence of food-products in the leucocyte, Metchnikoff[56] writes: "The digestion of proteid substances by the leucocytes is well shown by the gradual changes that take place in the muscular fibers which have been inglobed by leucocytes in cases of acute muscular atrophy. The presence of *peptone* in leucocytes, which has been so often proved by Hofmeister, is sufficiently accounted for by this fact of intracellular digestion, and need not, therefore, be referred, as done by this author, to an *absorption* by these cells of the *peptone formed in the alimentary canal.*" I need hardly observe, however, that, added to the foregoing testimony, Hofmeister's view seems sustained.

Indeed, the process to which the peptones owe their presence within the cell is not difficult to trace, if the latter's mechanical functions, as I have construed them, are taken into account. The presence of peptones within the perinuclear vacuole being an accepted fact (since it is recognized by both investigators), the presence therein of substances from which the peptones are elaborated must be accounted for. Metchnikoff traces these to products of degeneration, as suggested by his comparison, and perhaps to waste-products of digestion. Hofmeister's conception differs only from this in implying a closer or more direct relationship between the leucocytes and the intestinal contents of their host. In other words, while Hofmeister associates leucocytes with the process of digestion, Metchnikoff looks upon them only in the light of scavengers. That phagocytes may fulfill both rôles is obviously suggested not only by their own chemico-physiological characteristics, but also by their itinerary in the system. Both Hofmeister and Metchnikoff are right, therefore, each in his own way.

In his review of the absorption of proteids Stewart[57] writes: "Although a certain amount of egg-albumin and other native or slightly altered proteid substances can be absorbed as such by the small, and even by the large, intestine, there can be no doubt that the greater part of the proteids of the food is first changed into proteoses and peptones. But proteoses and peptones are absent from the blood, and, indeed, when injected into the blood they are excreted in the urine. When injected in larger amount they pass also into the lymph, from which they gradually reach the blood again, and are eventually, as before, eliminated by the kidneys. The clear inference is that when absorbed from the alimentary canal they must be changed into one or both of the chief proteids of blood and lymph (serum-albumin and serum-globulin) in their passage through its walls. And it has actually been shown that during digestion of a proteid meal the mucosa of the stomach and intestine contains proteose and peptone, while none is present in the muscular coat or in any other organ. They rapidly disappear from a portion of the mucous membrane kept at a temperature of about 40° C. outside the body; but not if it has been thrown into boiling water immediately after excision, nor even if it has been heated at 60° C. for a few minutes and then kept at 40° C. Now, a temperature of 60° C. does not destroy an unorganized ferment, but kills a *living cell.* The regeneration of the proteose and peptone must, therefore, presumably take place *in cells,* and the only available cells in this locality are those which line the intestine, or the *leucocytes* which wander between them. Accordingly, both have been credited with the power of absorbing and transforming these substances."[58]

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[56] Metchnikoff: *Loc. cit.*, p. 124.

[57] Stewart: "Manual of Physiology." 4th ed., 1900.

If my views concerning the functions of the epithelial cells of the intestines, as submitted in the seventh chapter, are sound, they subserve an entirely different function from that now generally ascribed to them: *i.e.,* that of supplying the intestinal tract with a secretion calculated mainly to asepticize the intestinal contents. On the other hand, I showed that the lymph-follicles, including Peyer's patches, supply leucocytes, formed in the cytogenic area of the follicles (Flemming's central nodule), to the intestinal cavity through the fenestrated membrane overlying each follicle. As the inquiry did not afford evidence to the effect that all these leucocytes served to insure destruction of pathogenic bacteria, I stated that *some* of them carried out this function. Indeed, there was good ground for this limitation, for I had already referred to the iron-laden leucocytes observed by Macallum and had been led later on to allude to those charged with the return of bilirubin to the circulation. That the leucocytes supplied to the intestinal canal by the cytogenic follicular areas include some—and probably a large proportion—whose functions it is to ingest proteids *with* the iron and bilirubin, then re-enter the intestinal wall by way of the villi, is very likely. To the various agencies thus incorporated in the organism can now be added that referred to by Metchnikoff in the sentence: "The presence of peptones in leucocytes which has been so often proved by Hofmeister." While this contributes further evidence to show that my conception of the whole process must be poised upon solid premises, it also suggests that leucocytes ingest *proteids*, and not peptones, from the intestinal canal, because peptones are the terminal products of the digestion of proteids.

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[58] All italics are my own.

If leucocytes ingest proteids, these must accumulate in their perinuclear vacuole and find their way into the nuclear canaliculi. These cells being freshly supplied to the intestinal canal from the follicles, the proportion of blood-plasma in them must be limited when, laden with proteids, they enter the venules of the villi to find their way to the portal vein. Even in this vessel they must again find a dearth of adrenoxidase, for we have seen that this channel is essentially venous. We must not lose sight of the fact, however, that potent additions to its contents are obtainable here: the spleno-pancreatic internal secretion, *i.e.*, trypsin, to which the plasma of arterial blood and dextrose may be superadded when the precincts of the hepatic artery, *i.e.*, the hepatic lobules, are reached.

If these cells do take up proteids and other bodies utilized in nutrition or in the building up of various organic structures, their own canaliculi, *i.e.*, those of the cell-substance, must serve as the eliminatory channels. In other words, proteids ingulfed by the leucocyte must be submitted to a process of digestion in the nucleus and its vacuole, and the products be passed out as granules. *This elevates leucocytes to the rank of glandular organs,* but we must not overlook the fact that glands in general supply their secretion in the form of granules. Referring to the parotid, for instance, Foster speaks of the secretion as "generally in the form of granules" and of the "granules" which in the submaxillary gland "may obscure the nuclei." The granules of the pancreas, of the intestinal epithelial cells, etc., are also familiar examples. Indeed, all these granules only differ from those of leucocytes in being less complicated molecularly and smaller. They seem to me fully to represent a true, cellular secretion.

What is the nature of the neutrophile's secretion, *i.e.,* the composition of its granules? Milroy and Malcolm[59] state that the finely granular amphophile (or neutrophiles) granules "are usually taken to be proteid in nature," and refer to the fact that Sherrington had suggested that they might be "of nucleoproteid nature": a view which their own researches confirm. Under the action of alcohol kept at boiling-point, neither fine nor coarse oxyphile granules were dissolved; ether also at boiling-point gave similar results. These agents being then used successively, the granules remained practically unaltered: a fact which leads the authors to conclude that the granules *cannot consist* of *fat* or *lecithin.* Weak alkaline solution at 115° to 120° C. almost entirely removed the granules from the finely granular cells, "but the most striking feature was the persistence of two structures, the nuclei and the coarse oxyphile granules." Solutions of sodium carbonate (½ to 1 per cent.), followed by careful washing, almost entirely removed the fine oxyphile granules in from one to sixteen hours, while the coarse ones were left. Oxalic acid (0.4 per cent. in alcohol, then 1¼-per-cent. watery solution) entirely removed the small granules, a few of the coarsely granular oxyphile cells containing pink-stained granules, while others were vacuolated. As a result of these tests (which should be read *in extenso* in the original paper) Milroy and Malcolm write as follows: "The possibility of both types of granules consisting of the same kind of organic matter either *differently bound* or with organic salts atached in such a way as to alter the solubilities is certainly a strong one. That it is not *simply* albumin or globulin appears evident from the comparatively insoluble character of both types of granules, but especially the coarse oxyphile ones. Again, the fact that the fine granules are not only oxyphile, but also basophile, supports the view that they are composed of a *complex proteid substance*."[60] . . . The concordance of these facts with those previously recorded appears to me conclusive.

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[59] Milroy and Malcolm: Journal of Physiology, vol. xxv, 1899.

Milroy and Malcolm's researches not only seem to me to give neutrophile granules their own identity (though showing a distinct kinship to the larger acidophile granules), but also to emphasize the fact that these minute masses of proteid substance represent the end-result of the intracellular process that occurs during the journey of the leucocytes from the intestinal villus to the general circulation *via* the portal and hepatic vessels.

Is it only in the cells that the reactions which serve to convert proteids into assimilable products occur? The investigations of Milroy and Malcolm will greatly assist us in elucidating this question.

In their first article on the "Metabolism of Nucleins"[61] these investigators say, in the course of a review of the metabolism of the nucleins under physiological conditions: "When nucleins are taken by the mouth, the first change that they undergo in the alimentary tract is a simple solvent one in the stomach, and that only to a very slight degree. They are never split up into their constituents. They are easily broken up, however, by the *pancreatic secretion*[62] into an organic phosphorus-holding acid (not nucleic acid) and albumose or peptone. The important points to notice are that the phosphorus is still in organic combination, and that neither ortho- nor meta- phosphoric acid is so formed. It is probable that the organic phosphorus-holding acid so formed is similar to thymic acid. It forms soluble compounds with albumose and peptone, and is, in all probability, so absorbed. After absorption the bodies derived from the nucleins cause a well-marked *leucocytosis*, and the excretion of phosphoric acid in the urine is increased. Whether a hypoleucocytosis *always* precedes the hyperleucocytosis is difficult to say. Almost all the writers on this subject have emphasized the fact that, on giving nucleins by the mouth, the phosphoric acid excretion in the urine is increased; but they have omitted to show that this excretion *cannot be accounted for* by the phosphorus taken in the form of nucleins, there being really more phosphorus excreted by the kidneys than was present in the original nucleins."

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[60] The italics are my own.

[61] Milroy and Malcolm: Journal of Physiology, vol. xxiii, No. 3, July 26, 1898.

[62] All italics are my own.

Again, as a result of a series of experiments, Milroy and Malcolm are led to the following conclusions among others: "1. The digestion products of nuclein-holding tissues, nuclein and nucleic acid, cause, on being absorbed, a temporary leucocytosis, which is accompanied by a rise in the P_2O_5 excretion above that derivable from the absorbed phosphorus. These alterations are especially well marked after giving nucleic acid. 2. The alloxuric bodies are excreted in excess, after nucleic acid has been given, and in all probability also after large doses of nuclein-holding tissues or nucleins, although in our experiments, owing to the small amount of thymus taken, there was no distinct increase. 3. The uric acid excretion after nucleic acid was only slightly, if at all, increased. We were exceedingly anxious to give larger doses of nucleic acid, but were unable to do so because of certain rather disagreeable symptoms (*severe muscular tremors*) which arose after the *larger* quantity had been given."

The augmented phosphoric acid excretion to which the authors refer, and which they state cannot be accounted for by the phosphorus taken in the form of nucleins, has doubtless suggested to the reader as primary cause the increased functional activity of the adrenal system induced by the phosphorus ingested: an interpretation sustained by the presence of severe muscular tremors, "which arose after the larger quantity had been given." Of course, phosphorus here acts like any other toxic as a stimulant, the anterior pituitary body responding to the effects of organic poisons as well as those foreign to the system as a chemical entity.

Still, this involves the necessity of showing that leucocytes are themselves the seat of the enhanced metabolism and the source of the excess of phosphoric acid to which the muscular tremors are due, in accord with my previous statements to that effect. Again, if, as I have suggested, the granules represent the leucocytic secretion, an excess of granules must occur under the influence of the stimulation of the adrenal system induced. That such is the case is shown by the following casual remark of Stokes and Wegefarth,[63] who, as stated, based their studies of the free granules derived from leucocytes upon examinations of blood taken from about five hundred persons: "In perfectly fresh specimens the granules were not numerous, but they seemed somewhat increased in patients who had been taking *tonics* or various alcoholic drinks."

This, in turn, involves a query as to the manner in which the anterior pituitary body becomes primarily stimulated when nucleins are taken in excess, for it would seem that locked up in the perinuclear vacuole of the leucocytes their phosphorus could not influence the adrenal system through the blood-stream. This would doubtless hold were the intracellular process to cease at any time, but, as this must begin as soon as the cells enter the hepatic capillaries, after acquiring therein their adequate supply of adrenoxidase, their normal production of granules must start at once. An inordinate proportion of nucleins in the food soon supplies the blood-stream, through the agency of the cells, with an abnormal quantity of these minute phosphorus-laden bodies. These at first give rise to excessive functional activity, including among other signs the "severe muscular tremors" to which Milroy and Malcolm refer, coupled with an excess of P_2O_5 production. Persisted in, however, the excessive (relative) ingestion of nucleins brings on, as do other toxics, adrenal insufficiency, which, by entailing a reduced production of adrenoxidase and trypsin, upon which the physiologically perfect intracellular reactions mainly depend, correspondingly lowers the efficiency of the cleavage-processes. This means, instead of the physiologically perfect granules which, we have seen, Milroy and Malcolm found to be proteid in nature, an accumulation in the blood of proteid toxalbumins.

In their first paper, the above-mentioned investigators draw attention to the two decomposition products considered "as more or less characteristic signs of the decomposition of the nucleins, viz.: the alloxur bases and phosphoric acid." If my conception as outlined in the preceding paragraph is justified, these alloxuric bases are products of *inadequate* metabolism, while phosphoric acid is the product of perfect metabolism. Uric acid having likewise been considered as a product of the complete process, a rise of alloxuric excretion cannot occur along with excessive phosphoric acid production. That my conclusion, based mainly on Horbaczewski's work, was warranted, is shown by what Milroy and Malcolm term "points of special importance" as results of a series of experiments, namely: "1. There is no doubt that the P_2O_5 excretion is increased even when very small doses of thymus are given. 2. Relatively, also, the P_2O_5 is increased in proportion to the nitrogen. 3. With the small amount of thymus taken there was practically no appreciable alteration in the excretion of the alloxuric bodies, either absolutely or relatively to the total nitrogen or total P_2O_5." All this serves to emphasize another feature of the problem: *i.e.*, that *phosphoric acid is the prototype of uric acid as a product of perfect or physiological intracellular metabolism, and that the phagocytic leucocytes which take up nucleo-proteids from the intestinal food-products are the seat of the reactions through which these bodies are converted into assimilable products.*

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[63] Stokes and Wegefarth: *Loc. cit.*

Although I have only dwelt so far, as regards the intracellular processes with which nucleo-proteids are concerned, with neutrophile leucocytes, these are not alone the seat of reactions which, normally performed, end in the production of uric and phosphoric acids. Indeed, we have seen that all leucocytes contain nuclein in their "nucleus"—a fitting name under the circumstances, and the physio-chemical process reviewed only typifies that which occurs in all varieties of leucocytes. Wherein the neutrophile cells are distinguishable, however, is in their ability as phagocytes to take up nucleo-proteids from the intestine, and to break them up, by means of the trypsin and adrenoxidase subsequently absorbed by them, into peptone and an organic compound containing phosphorus.

How are the various bodies, the presence of which this suggests, utilized? The presence of pancreatic secretion in the intestine, and of the spleno-pancreatic secretion in the portal vein, would suggest that the leucocytes must be carriers of carbohydrates: an important question when we consider the leading functional rôle which myosinogen plays in muscular contraction. Dextrose, formed from glycogen, itself in turn a product derived from starches, forms part of a chain of events which would, in a measure, have to occur within the cell itself. That such is the case is suggested by the investigations of Zabolotny,[64] who found that phagocytes devoured particles of starch-paste and digested them: features which led this investigator to conclude that "the presence of an amylolytic ferment in the phagocytes cannot be doubted." But Zabolotny likewise states that when leucocytes ingest starch they become iodophile. This, as is well known, has been termed by Ranvier and other physiologists the "*glycogen* reaction."

Foster, referring to this question, says: "In the case of many corpuscles, at all events, we have evidence of the presence of a member of the large group of *carbohydrates,* comprising starches and sugars, viz.: the starch-like body *glycogen.* . . . This glycogen may exist in the living corpuscle as glycogen, but it is very apt, after the death of the corpuscle, to become changed by hydration into some form of sugar, such as maltose or dextrose." Indeed, he furnishes us complementary evidence, alluding to the cellular proteids in the following sentence: "One of these proteids is a body either identical with or closely allied to the proteid called *myosin,* which we shall have to study more fully in connection with muscular tissue." I have shown that myosin is the *post-mortem* product of the action of what remains of oxygen in the plasma upon myosinogen, and that this is the cause of *rigor mortis.* Foster says, in this connection: "And we have reasons for thinking that in the living white corpuscle there does exist a body identical with or allied to *myosinogen,* which we may speak of as being in a fluid condition, and which, on the death of the corpuscle, is converted, by a kind of clotting, into myosin, or into an allied body which, being solid, gives the body of the corpuscle a stiffness and rigidity which it did not possess during life." All this seems to me clearly to suggest that these leucocytes, in the light of my views, supply the muscle-cells of the entire organism with myosinogen.

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[64] Zabolotny: Russian Archives of Pathology, April, 1900.

Still, our analysis alone so far points to the neutrophiles —by far the most numerous leucocytes in the blood-stream—as the ones upon which this great function would devolve. It becomes necessary, therefore, to control this conclusion by showing that excessive muscular exercise, by creating a demand for myosinogen in the cells of all muscles,—skeletal, cardiac, vascular, etc.,—engenders a leucocytosis in which the neutrophiles prevail. The data for this are available in a study of this subject by R. C. Larrabee,[65] who writes as follows: "The paper is based on a study of the blood of four of the contestants in the Boston Athletic Association's Marathon race of 1901. This is a road-race of about twenty-five miles (40 kilometers), held each spring. The severity of the contest will be apparent when it is said that the winner—not included in my four—covered the distance in less than two and one-half hours. This is about ten miles an hour, about as fast as an ordinary man rides his bicycle for pleasure. . . . The blood of these four cases [counted by the author, assisted by Dr. W. H. McBain] before the race showed no abnormalities. The percentage of polymorphonuclear neutrophiles may perhaps run a little high, but this is to be expected in active young men in the best possible physical condition. After the race the blood was taken immediately, within five minutes from the actual finish. In every case a leucocytosis was found, varying from 14,400 to 22,200. The differential count showed that the increase was *mainly* in the polymorphonuclear *neutrophiles*."

That the exciting cause of the leucocytosis was the increase of waste-products which in turn stimulated the adrenal system, hardly needs to be dwelt upon. Vagal influence incited to inordinate activity and controlled the organs charged with the genesis of these particular cells, while the inordinate oxidation processes started by the overactive adrenals in all tissues accounts for the general leucocytosis which the word "mainly" implies.

Myosinogen being a member of the globulin group of proteids, the other members of this group should be represented among the cell's products, particularly fibrinogen found in the blood-plasma in association with serum-globulin and serum-albumin. That such is the case is demonstrable. Stewart[66] alludes to the sources of nucleo-proteid in the following words: "In shed and clotting blood, the only possible sources of nucleo-proteid, so far as we know, are the corpuscles and the blood-plates. The red corpuscles we may at once dismiss, for, although they contain a small amount of nucleo-proteid, not only do they remain intact under ordinary circumstances during coagulation, but there is the strongest evidence, as has already been pointed out, that they do not make any essential contribution to the process. We have left over the leucocytes and the platelets. The latter are said and the former are known to yield *nucleo-proteids* when they are broken up in the laboratory; and it is highly probable that from both, but especially from the white corpuscles, nucleo-proteid is liberated in the first moments after blood is shed, and that this nucleo-proteid *is then changed into fibrin-ferment.*"

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[65] R. C. Larrabee: Journal of Medical Research, Jan. 1902.

The relationship between the cellular nucleo-proteids and fibrin which this quotation suggests finds itself sustained by Ranvier,[67] who, alluding to the rôle of granules in the formation of fibrin, says: "Free granulations, which we found in the blood besides the red and white corpuscles, are very numerous; they were termed 'elementary vesicles' by Zimmermann. In a preparation of human blood examined after rouleaux of red corpuscles have formed these granulations may easily be observed, two varieties being distinguishable. The first are spherical, small droplets of fat; the others are angular or variable in shape, and appear at first as if they were fragments of white corpuscles, but differ from the latter in not being altered by water. They are *stained by iodine,* but remain colorless in carmine solutions. We will see that these are also the characteristics of fibrin." After reviewing the phenomena that attend coagulation, and exposure by washing of the fibrinous net-work, he says: "When this preparation is examined and magnified four hundred to five hundred diameters, the fibrinous reticulum can be seen distinctly, and is disposed in a very interesting manner: From an angular granulation, from 11 to 10 μ in diameter, very tenuous fibrils start divergingly, then subdivide, to unite with other fibrils, in order to form a delicate net-work. The preparation is covered with these small net-works, each of which has its central granulation. . . . The granulations which serve as centers for each diminutive fibrinous reticulum have the same microchemical properties as the fibrils."

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[66] Stewart: *Loc. cit.*
[67] Ranvier: *Loc. cit.*, 213.

A normal deduction which seems to me to impose itself in this connection is that fibrin is to the blood what myosin is to the muscle-cells, *i.e.*, a post-mortem product due to arrest of the oxidation process which during life is insured by the adrenoxidase—the supposed "fibrin-ferment." In other words, it not only becomes probable that *peptones, myosinogen, and fibrinogen are products of the same variety of leucocyte, the neutrophile, and therefore chemically similar when liberated from the latter,* but also that *fibrinogen subserves the same purpose in the blood that myosinogen does in muscle:* i.e., *it supplies it with its primary source of functional energy.*

True, the solubility of fibrin differs somewhat from that of myosin, but this is probably due not to a difference in the molecular structure of fibrinogen as against that of myosinogen, but to the influence of the medium in which the granules are dropped by the leucocyte. Indeed, the ashes of fibrin contain a larger proportion of calcium and magnesium phosphate than does myosinogen.

Another conclusion which now seems warranted is that *the neutrophile leucocytes are the agencies which take up proteids in the intestinal canal, and, after submitting them to a process in which various physio-chemical bodies taken up by them in the portal and hepatic systems take part, distribute the products to every part of the organism, including the blood itself.*

Such being the case, the proteids, inclosed in their diminutive carriers, should not be found in the blood of the portal system. Foster writes, in this connection, after referring to the difficulties attending the experimental determination of the path taken by proteids: "Bearing this in mind, we may state that all observers are agreed that peptone is absent from chyle, or at least that its presence cannot be satisfactorily proved. On the other hand, while some observers have succeeded in finding peptone in the portal blood after food, but not during fasting, many have failed to demonstrate the presence of peptone in the blood either of the portal vein or of the vessels at large, *even after a meal containing large quantities of proteids.*" Again: "If an artificial circulation of blood be kept up in the mesenteric arteries supplying a loop of intestine removed from the body, the loop may be kept alive for some considerable time. During this survival a considerable quantity of peptone placed in the cavity of the loop will disappear: *i.e.*, will be absorbed, but *cannot be recovered from the blood* which is being used for the artificial circulation, and which escapes from the veins after traversing the intestinal capillaries. The disappearance is *not due to any action of the blood itself,* for peptone introduced into the blood before it is driven through the mesenteric arteries in the experiment may be recovered from the blood as it escapes from the mesenteric veins. It would seem as if the peptone were changed before it actually gets from the interior of the intestine into the interior of the capillaries."[88] Viewed from my standpoint, *the peptones are hidden in the neutrophile leucocytes which the follicles of the segment continue to produce. These cells, after migrating over the serum-bathed (and thus constantly asepticized) epithelial surface, and ingesting their burden, find their way into the villi's venules and thence into the mesenteric channels.*

If the foregoing analysis and the various deductions submitted are sound, the neutrophile leucocytes must fulfill a rôle in the organism commensurate with their relative proportion in the blood-stream. Indeed, the following conclusion appears to me to have been sustained:—

The neutrophile leucocytes, through the intermediary of their granules, the β granulations of Ehrlich, supply (1) the blood and all tissues (excepting the nervous system) their nutritive elements: i.e., *peptones; and (2) the muscles and the blood, the compounds from which they obtain their mechanical energy when exposed to the action of the adrenoxidase:* i.e., *myosinogen and fibrinogen.*

Ehrlich's Eosinophile Leucocytes.—Metchnikoff does not grant Ehrlich's eosinophiles phagocytic properties, these cells being unable to inglobe foreign bodies. Again, as emphasized by Ehrlich, the granules of these cells are only stainable with acid dyes, the other varieties either taking only alkaline dyes or simultaneously, as does the neutrophile just reviewed, both acid and alkaline dyes, etc. This marked affinity for acids obviously gives the eosinophile an identity of its own, while its non-phagocytic functions as clearly separate it from the finely granular cell just reviewed, which is essentially phagocytic. Ehrlich's eosinophile is usually considered under the heading of "coarsely granular oxyphile cell."

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[88] All italics are my own.

These cells only represent from 2 to 4 per cent. of all the leucocytes in the blood-stream, but this proportion is rapidly increased during disease. Kanthack and Hardy, in the article previously quoted, describe them as follows: "The coarsely granular oxyphile cell, or eosinophile cell, varies in size in different animals, not only absolutely, but relatively to the dimensions of the other classes of cells. In man it is larger than either the hyaline cell, the finely granular oxyphile cell or the finely granular basophile cell. In the rat, rabbit, and guinea-pig, on the other hand, it is smaller than the largest hyaline cells, but larger than the finely granular oxyphile and basophile cells.

"The *nucleus* is typically an elongated body bent to form a horseshoe. In the rat the arms of the horseshoe are carried so far round that in film preparations the ends often overlap, giving to the nucleus the appearance of a circle with a large hole in the center. Sometimes the nucleus is lobed; but we are inclined to regard this appearance as being largely due to the stresses to which the nucleus is subjected when the cell is dying. In the living cell at rest, when it is spherical, the shape of the nucleus, so far as it can be determined by the disposition of the cell-granules, is a simple horseshoe or crescent. A distinct nuclear net-work is present.

"*Cell-granules.*—The cell-granules are relatively large, spherical, or slightly ovoid bodies, and are sharply marked off from the cell-substance by their *very high refractive index,* which is so great that in fluid preparations the granules have a *brilliant, greenish luster.*[69] The cell-substance in which they are imbedded has the appearance of a clear, transparent, structureless jelly. The intensity of the oxyphile reaction of these granules differs in different animals, but is always high. Thus, it is very high in the case of the granules of man, these staining with eosin dissolved in 95 per cent. alcohol. . . . The granules also stain with weak acid dyes, such as Orange *G*, hæmatoxylin, and sodium sulphindigotate. Ehrlich-Biondi's mixture (washed out with 95 per cent. spirit) colors these bodies brown-purple, and the 'neutral' mixture (washed out with water) stains them a very intense purple. Corrosive sublimate increases the oxyphile reaction, as does also heat when applied to the dried film."

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[69] All italics other than those of the side headings are my own.

Gulland found Heidenhain's iron-hæmatoxylin extremely valuable to counteract "the bright refraction of the granules" which "blinds the eye to the presence of the threads" (my canaliculi). The granules are stained opaquely in shades of black and gray. He was thus able to ascertain that the granules varied greatly as to size, the smallest granules lying close to the astrosphere and the larger at the periphery, the arrangement pointed out by Heidenhain and shown in Figs. 10, 12, and 16 of Gulland's plate. In the newt's blood, as already stated, "these cells are markedly amœboid, and have the habit of throwing out circular pseudopodia, which are often connected to the main part of the cell only by a very delicate thread." Gulland illustrates this feature in Figs. 3 and 6 of his plate, and states that "it is evident that the threads are often broken through and the spherical portion of the cell-body set free, as the blood contains a large number of them." He also refers to the fact that, "when the eosinophile cells are found degenerated in blood or pus examined in the fresh state, the granules are always in the Brownian movement."

In the study of the granules of neutrophile cells I referred to the chemical analysis of Milroy and Malcolm and to various points of dissimilarity between these cells and the coarse oxyphiles now in question. Considered from the standpoint of the latter, these investigations showed that, while neither alcohol nor ether, nor both of these agents used successively, produced alterations in either variety, the failure of the latter process *excluded* the possibility of their consisting of *fat* or *lecithin.* Weak alkaline solutions at about 120° C. caused (a feature referred to by the authors as striking) the removal of practically all the granules of the finely granular cells (the neutrophiles), and "persistence of two structures, the nuclei and the coarse oxyphile granules." Acetic acid in alcoholic solution and oxalic acid caused partial removal of both granules, but "sodium ethylate in alcoholic solution removed the fine oxyphile granules almost completely and only affected the coarse ones to a slight extent."

The authors, while concluding that the granules might also be nucleo-proteid in nature, *i.e.,* similar to those of the neutrophile cells, account for the discrepancies in the results of their analyses by the following argument: "The fact that weak acid solutions dissolve both types of granules at least partially is not against the view that they are nucleo-proteid in nature, because these bodies are more easily soluble in weak acid solutions than almost any other complex proteid. The fact that some granules are undissolved, while others are removed, is probably due to the fact that the former have undergone coagulation, while the latter have been rapidly fixed, although it may be also due to the nature of the salts which are combined with the proteid."

Still, the very high refractive index to which Kanthack and Hardy and Gulland refer is not characteristic of the neutrophile granules, and this seems to me to testify against an absolute functional similarity between them and the granules of the eosinophiles. Indeed, with the plasma as excipient for the adrenoxidase, we can as readily account for the presence of the "brilliant, greenish luster" witnessed by the above authors as we can for the phosphorescence of the photogenic organs of lightning-bugs: *i.e.,* by the simultaneous presence of phosphorus and oxygen. This seems to me to indicate that we are dealing with a nucleo-proteid body, as Milroy and Malcolm contend, but with one richer in phosphorus than that forming the neutrophile granules.

What are the functions of the eosinophile leucocytes in the organism? The high percentage of phosphorus in their granules suggests the possibility of their being lecithin carriers; but we have seen that the investigations of Milroy and Malcolm clearly show that this organic body is absent. L. F. Barker,[70] of Baltimore, noted the presence of iron in the granules of the eosinophile leucocytes,—a point which he thinks may be of some value in determining the significance of the leucocytic granulations,—but we cannot consider them as the cells intrusted with transportation of iron from the intestine, for they are not phagocytic. Indeed, it has now become evident that the neutrophiles are intrusted with this function, for Macallum used albuminate of iron. The intestinal leucocytes of his previously starved animals evidently took this substance up as they would the proteids of their usual food. Barker's observation, however, adds another link to the chain of evidence which unites the eosinophiles to the neutrophiles, for, in addition to being both nucleo-proteid carriers, they now become also iron carriers. By tracing the itinerary of this iron we may, therefore, obtain a clue to the true identity of its cellular host.

The phagocytes seen by Macallum to ingest the albuminate of iron being assimilated to those charged at all times with the duty of selecting proteids from the intestinal foodstuffs, it becomes a question as to where they can part with their iron in order to facilitate its absorption into the hæmoglobin molecule, of which, as is well known, it forms an important constituent. From the intestine the iron is carried to the portal system, thence into the hepatic lobule. It must be here that the phagocytic leucocytes must take part in some process related to the elaboration of hæmoglobin, for we have seen on page 335 that in the spleen the leucocytes are formed *in situ*, pass out into the pulp-channels, take up the iron-pigment (probably that of disorganized red corpuscles), and carry it to the liver. Again, and for reasons which are there given, I was led to conclude (page 339) that bilirubin and iron were used to build up the hæmoglobin in the lobular (hepatic) capillaries. The liver, therefore, seems to receive iron from both directions—intestine and spleen—a normal mechanism when we consider that the liver's blood passes almost directly to the heart, and thence to the lungs.

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[70] L. F. Barker: Johns Hopkins Hospital Bulletin, Oct., 1894.

How do the eosinophile (*non-phagocytic*) leucocytes acquire their iron? We can hardly imagine that when the splenic or intestinal leucocytes reach the hepatic lobule their contents or any part thereof is disgorged to enable another cell to appropriate it. Indeed, there is not the slightest evidence that such a process occurs, although the eosinophile has already been shown to contain not only iron, but also the other main constituents of the neutrophile cell. There exists a physiological process, however, through which the eosinophile can acquire all the attributes of the latter: *i.e.*, by mitosis, a mode of cell-multiplication known to apply to leucocytes and particularly to neutrophiles. Gulland refers to this feature in the following lines: "The cells which one sees dividing or about to divide have generally the appearance of medium-sized hyaline cells, with a relatively large, rounded nucleus and a comparatively small cell-body, in which the mitoma is not easily made out. But there is no doubt that cells with horseshoe-shaped nuclei [the eosinophiles] divide, and that the nuclei may even advance as far as the spirem stage without altering their shape. Cells with more markedly polymorphous nuclei, as, for instance, the *ordinary oxyphile cells*, certainly divide also, but they seem generally to go through a preliminary resting stage in which the polymorphous nucleus returns to the rounded form."

In Gulland's plate, Figs. 3 and 6, which refer to eosinophiles from newt's blood, graphically portray a secondary process through which these cells can subdivide, or rather yield a portion of their substance. In 3, a spherical pseudopod is in the act of being formed; in 6, three similar masses appear, the lowest of which is on the point of being separated by the mother-cell. Referring to the bridges that connect net-works of granules with basophile leucocytes, Gulland remarks: "I have little doubt that when that stage is reached [he associates the phenomenon with a supposed process of degeneration] these bridges are torn across and the granules are actually left behind. This forms an exact parallel to what happens in the *eosinophiles* of the newt's blood."

It thus becomes evident that recognized cytological phenomena sustain the conclusion that *neutrophile leucocytes are* *the parent-cells of eosinophile leucocytes,* and that *eosinophiles can part with segments of their cell-substance.*

But does the process of neutrophilic mitosis actually occur in the liver? M. Duval,[71] in his study of the hæmatopoietic functions of this organ, refers to the proportion of the red to the white corpuscles in the blood of the portal vein as compared to that in the hepatic vein, and writes: "Researches in this connection give as result: 1 white corpuscle to 746 red in the *portal* vein, and 1 white corpuscle to 170 red in the *sub-hepatic* veins. This difference can only be due to a production of white corpuscles in the liver or to a destruction of red corpuscles." That red-corpuscle destruction is a function of the spleen is sustained by the presence "in the spleen-pulp," using Foster's words, of red corpuscles "in various stages of disorganization, some of them lying within the substance of large colorless corpuscles, and, as it were, being eaten by them." The presence of blood-pigments in the liver has been thought to indicate that red corpuscles were destroyed in this organ; we have seen, on the contrary, that it is the seat of a reconstructive process of which hæmoglobin is the product. Though the liver may be a seat of destruction for red-cell fragments, the likelihood that any entire corpuscle leaves the capillaries of the hepatic lobules to penetrate the cells is so remote that it can be left out of question. On the other hand, we have seen that these capillaries are the seat of the more important processes connected with the blood. It seems probable, therefore, that the liver, owing in part to the inordinate temperature of its lobular channels (106° F.; 41.9° C.), is also the seat of the mitotic process.

"At a certain period," write Böhm, Davidoff, and Huber,[72] "the embryonic blood consists principally of nucleated red cells, which proliferate in the circulation by indirect division. The colorless blood-cells, the development of which is not yet fully understood, appear later. It is possible that they also are elements of the blood-islands, which do not contain any hæmoglobin. In a later period of embryonic life the liver becomes a blood-forming organ. Recent investigations have shown, how-over, that it does not take a direct part in the formation o the blood, but only serves as an area in which the *blood-corpuscles proliferate* during their slow passage through its vessel The *blind, sac-like endings of the venous capillaries* seem to b particularly adapted for this purpose, as in them the blood current stagnates, and it is here that the greater number o blood-cells reveal mitotic figures. The newly formed element are finally swept away by the blood-stream and enter the general circulation."

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[71] M. Duval: "Cours de Physiologie," p. 200.

[72] Böhm, Davidoff, and Huber: *Loc. cit.*, p. 168.

Gulland likewise states that the eosinophile cell is derived from the "finely granular acidophile" (the neutrophile), and the latter is itself traced back to the lymphocyte. "The transition-forms between the finely granular and the coarsely granular acidophile cells are seen much more frequently in the bone-marrow than in the blood," says this investigator, "and it seems certain that both from this source and from mitotic division the main source of the eosinophile cells is in the bone-marrow." That there is ample margin for my view that mitosis may occur in the liver is also suggested by the following additional lines: "They must arise *elsewhere*, however, *in abundance*,[73] for Schaffer[74] and I[75] have shown that they are present in the thymus and in lymphatic glands before either bone or bone-marrow is properly formed at all, and Engel[76] has seen them in the chick's blood on the fifth day of incubation. In the transition-forms (see Figs. 2, 8, 11) there is little in the general shape of the cell and nucleus to distinguish them from the preceding stage." All the evidence tends to show, therefore, that *the process of mitosis, through which eosinophile leucocytes are formed from neutrophile leucocytes, is carried on in the capillaries of the hepatic lobules, though it can also occur elsewhere in the organism.*

I have referred to the direct path which leucocytes can follow from the liver to the heart and thence to the lungs. If eosinophiles are formed in the liver, therefore, the lungs should show indications of the presence of these leucocytes. Proof that such is actually the case is obtainable with the aid of pathology: *i.e.*, the significant fact that in several pulmonary diseases eosinophile cells are to be found in the sputum. Teichmüller,[77] for instance, has not only found this to be the case in pulmonary tuberculosis, but considers an increase of these cells favorable from the standpoint of prognosis. In asthma, though a non-ulcerative process is present, eosinophiles are to be found in abundance in the sputum, and Gollasch[78] states that they are connected with the formation of the Charcot-Leyden crystals. Lenhartz[79] states that "it is not improbable that the majority of cells designated as 'alveolar epithelia' are variously altered forms of leucocytes. The protoplasm very frequently shows fine or *coarsely granular* fatty metamorphosis, which is characterized by the *strongly refractive index*."

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[73] The italics are my own.
[74] Schaffer: Centralbl. für die med. Wissen., 1891.
[75] Gulland: Journal of Path. and Bacteriol., 1894.
[76] Engel: Archiv f. mikr. Anat., vol. lxiv, 1894.

The irregularity of the granules, and the manner in which they form fibrin, as described by Ranvier, and the peculiar color of the granules are recalled by the following description of the Charcot-Leyden crystals by Lenhartz: "The Charcot-Leyden crystals are delicate, very sharply pointed octahedra which occur in very variable size. They present a sometimes water-clear, transparent, sometimes a slightly yellowish-green, Rhine-wine color; they occur either isolated or in dense collections which here and there are jumbled together, or in uniform rows, following the mucous shreds." The same author also says: "The crystals were first found in the sputum by Friedreich in croupous bronchitis. On the other hand, Leyden has drawn attention to their frequent occurrence in asthmatic expectoration."

The association with various pulmonary diseases obviously suggests that their presence is pathological, whereas we consider their presence in the lung as normal, and their *elimination* in their recognizable form as an accompaniment of the morbid state. That such is the case is shown by the fact emphasized by Lenhartz that: "The longer the asthmatic subject *is free from* paroxysms,—that is, the more time allowed for the formation of the crystals,—the more densely the spirals are studded with these crystals."

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[77] Teichmüller: Lenhartz's "Manual of Clinical Microscopy" translation by H. T. Brooks, 1902.

[78] Gollasch: Fortschritte der Med., vol. 1889.

[79] Lenhartz: *Loc. cit.*

While all these facts sustain my opinion that the lungs show ample evidence of the presence in them of eosinophile cells and of their granules, their identity as offsprings of the neutrophiles should be demonstrable here, as elsewhere, through their chemical properties. Indeed, their identity as daughter-cells of neutrophile leucocytes does not disappear even in the lungs, for both acids and alkalies can dissolve them, while the test common to both neutrophile and eosinophile granules, *i.e.*, insolubility in alcohol, is also applicable here. Lenhartz not only confirms this assertion by saying, in reference to the crystals: "They are readily dissolved in warm water, acids, and alkalies, but are *insoluble*[80] in alcohol"; but we also, it seems to me, can consider, as confirmation of my interpretation of the identity of the granules from which the crystals were derived, his statement that: "fixation of the air-dried preparation for one hour in absolute alcohol and subsequent staining with Chenzinsky's *eosin*-methylene-blue solution also gives very good results."

All these facts further confirm the origin of the eosinophile leucocytes from the liver, for there is no other path that would have brought them to the lungs. They also seem to me to indicate that, *after their formation by mitosis in the liver, eosinophile leucocytes are carried to the pulmonary lobules.*

This question has already engaged the attention of pathologists, including Virchow, Wagner, and Cohnheim. Lenhartz's view is fully sustained by my own investigations, however, when he says: "It is not improbable that the majority of the cells designated as '*alveolar* epithelia' are variously altered forms of leucocytes. The protoplasm very frequently shows *fine* or *coarsely* granular fatty metamorphosis, and is characterized by the strongly *refractive index.*" Again, while Lenhartz expresses his belief that the positive identification of the "alveolar epithelia" is "extremely difficult," he states that he understands thereby "the large oval or round polygonal cells, three to six times as large as a white blood-corpuscle, which are found in almost every sputum. The usually large cell-body is *coarsely granular,* and contains one or several vesicle-like nuclei." The true identity of epithelium of the alveoli and, therefore, of the lobule of which they form part now seems clear, if interpreted in the light of the data I have submitted: The cells to which Lenhartz refers, *i.e., the lobular epithelial cells, are aggregates of the polynuclear neutrophiles and of the daughter-cells of the latter, the eosinophiles.*

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[80] These italics are Dr. Lenhartz's.

We have seen that the neutrophiles start from the intestinal canal; that Macallum and L. F. Barker found leucocytes gorged with iron in this region, and, finally, that *some* bilirubin at least is recovered from the intestine—obviously, now, by leucocytes. We have traced the latter from the intestinal canal, through the portal system, liver, hepatic veins, heart, thence to the alveoli. After giving the formula of hæmoglobin, Foster writes: "It will thus be seen that hæmoglobin contains, in addition to the other elements usually present in *proteid* substances, a certain amount of *iron,* that is to say, the element iron is a distinct part of the hæmoglobin molecule, a fact which of itself renders hæmoglobin remarkable among the chemical substances present in the animal body." Kanthack and Hardy noted, as previously stated, that "in fluid preparations the granules have a brilliant, greenish luster"—a characteristic of fine hæmoglobin crystals. Hæmoglobin is readily soluble in blood-serum, as are the granules, we have seen. Ether coagulates hæmoglobin; it caused, in Milroy and Malcolm's experiments,[81] the granules to lose a part of their refractive power, even when boiling ether was used. The proteid constituents of the granules of the neutrophiles, myosinogen and fibrinogen, belong to the globulin group.

This recalls my statement in the first edition of this work (p. 441), in respect to the manner in which the heart-muscle was nourished: "Paradoxical as the statement may seem, I was led to conclude that the minute granules referred to on page 433"— a general outline of the prevailing views concerning the histology of the myocardium, in which the minute pigment-granules, easily seen therein microscopically, are mentioned— "were actually supplied to the heart through the intermediary of leucocytes. These cells were found to migrate from the liver (also through the hepatic veins) to the inferior vena cava, where they meet the adrenal secretion and proceed with it to the right ventricle."

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[81] Milroy and Malcolm: *Loc. cit.*, p. 112.

We can now understand how the granules of the neutrophiles are supplied to the muscle-fibers by quoting another of my statements (see page 434) concerning the distribution of fluids in the intimate structure of the heart: "Fluids can penetrate through the maze of cellular tissue to the bare muscular fibers; the sheaths that include the columns or chains of muscular bundles afford a peculiar system of canalization through which the liquids can easily gain access to them. The canals—the lacunæ of Henle—are the intervals *between* the columns of secondary bundles, or their sheaths, rather, which are placed in longitudinal apposition. Schweigger-Seidel and Ranvier having observed that interstitial injections of colored substances penetrated the *lymphatic vessels,* the lacunæ have been considered as adjuncts, or *extensions,* of the latter." In this sense, therefore, the Thebesian channels are adjuncts of the lymphatic system, for it is through their intermediary that the lacunæ of Henle are supplied with myosinogen granules and —a feature I wish to emphasize—their nutritional peptones and their fibrinogen. All of these jointly supply the heart with its working energy, when acted upon by the adrenoxidase of the blood-stream, and, as is the case with all the organs previously reviewed, by the thyroiodase also contained in the red corpuscles.

The bulk of the venous blood which enters the heart is sent, we have seen, along with its adrenal secretion and its leucocytes—neutrophile and eosinophile—to the lungs, Virchow, Friedreich, Leyden, Cohnheim, Wagner, Lenhartz, and other investigators having found them in the sputum, and histology having demonstrated their presence in the alveoli. Again, the path for these leucocytes from the intestine to the true respiratory areas of the lungs is comparatively direct: features which distinctly suggest that the protective functions in the respiratory tract resemble those in the intestinal canal, as regards the eosinophilic granules and the phagocytic functions of the neutrophiles, both kinds of cells being present, as we have seen. Of course, the intestinal lymph-follicles being the source of these cells, another arrangement prevails in the pulmonary lobules: *i.e.,* that to which we referred on page 713, to the effect that the lobular epithelium *per se* is an aggregate of neutrophiles and eosinophiles.

We can readily understand, now, why the eosinophiles deplete themselves of their granules in the alveoli: *i.e.*, to dissolve them in the plasma prior to their absorption by the red corpuscles. Indeed, the reticular structure of red corpuscles, "the same as that of colorless blood-corpuscles,"[82] observed by Louis Elsberg in 1879, seems to me to present all the features that have led me to consider as canaliculi the threads that constitute this reticulum in the latter cells. That the red-corpuscle "granulations," "platelets," or "hæmatoblasts" derived from them are mere droplets of adrenoxidase poured out through these canaliculi is shown by the fact that the characteristic affinity (requiring oxygen and alkaline salts, according to Ehrlich) for methylene-blue again appears: *i.e.*, as manifested by the deep-blue stain which we found in other structures, the axis-cylinder, neuroglia, etc., and in the leucocytes themselves. This fact was also noted by Litten.[83] That the droplets pass out through centrifugal channels in the cell, and that the latter presents the general mechanical characteristics of leucocytes, is also suggested by the researches of Hirschfeld,[84] who observed that the "blood-plates" are first seen as circular disks occupying the center of the cell, then move very slowly toward the periphery, and finally drop out of the cell through a minute aperture, which closes up again. As the "plate" leaves the cell the external portion gradually increases in size and is connected with the rest by a thread. Several of these may leave the cell together from different parts of the periphery. He also found them to stain with methylene-blue and hæmatoxylin. It is evident that we have in the red corpuscle a diminutive nucleated sponge capable of absorbing hæmoglobin from the serum of the pulmonary alveoli and of dealing it out in the blood-stream as needed by the tissues.

This feature and the functions of the leucocytes just described introduce complemental factors in the respiratory process as I interpreted it in the second chapter. It now seems to me that the whole process is summarized in the following conclusions:—

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[82] M. L. Holbrook: "Proceedings of the American Microscopical Society," vol. 1894.

[83] Litten: Deutsche med. Wochenschrift, Nov. 2, 1899.

[84] Hirschfeld: Virchow's Archiv, vol. clxvi, 1901.

1. The true respiratory areas in the pulmonary lobules are composed of the alveolar endothelial plates (the non-nucleated epithelium) and groups of eosinophile leucocytes (the nucleated epithelium) interposed between the former.

2. The eosinophile cells are the bodies in which hæmoglobin is formed from the proteids, bilirubin, and iron absorbed by their parent-cells, the neutrophiles, in the intestinal canal.

3. When the eosinophile leucocytes reach the alveoli from the liver viâ the heart they assume an orderly arrangement and alter their shape, so as to form the alveolar epithelium.

4. The eosinophile leucocytes supply the adjacent plasma with their hæmatin, and the latter is absorbed by the underlying red corpuscles along with the oxygenized secretion (adrenoxidase) to form hæmoglobin.

5. Leucocytogenesis being governed by the adrenal system, the main factors of the above respiratory process, the production of eosinophile cells and of adrenal secretion, are thus dependent upon the functional integrity of this system.

6. The neutrophile leucocytes which accompany the eosinophiles migrate from the capillaries of the pulmonary artery to the perialveolar lymphatics, and supply the interlobular structures with their nutritional and functional elements: i.e., *peptones, myosinogen, and fibrinogen.*

7. During certain diseases neutrophile and basophile leucocytes may also penetrate into the alveoli and be found in the sputum.

THE BASOPHILE LEUCOCYTES.—These cells show the division into two groups, "finely granular" and "coarsely granular," which characterizes those just reviewed. They seem to differ from the latter in every other way, however, for, while these are amœboid, basophiles are not considered so by most histologists. Gulland—rightly, in my opinion—contends that they are, the variations of shape that they show and the manner in which they are scattered throughout the body being adduced as main reasons. The nucleus is round, oval, or kidney-like; is less clearly differentiated from the cell-substance, and stains with much greater difficulty than that of the neutrophile.

As regards their distribution, Ehrlich and Ranvier found them in the peritoneal, pleural, and pericardial cavities, and also in the connective tissue, but, as emphasized by Kanthack and Hardy, the cells in the connective tissue differ somewhat in shape and size from those in the three cavities mentioned. The latter investigators also found the coarsely granular basophiles "exceedingly numerous in connective-tissue spaces, where they form sometimes an almost complete sheath for the *lymph*-capillaries." Their distribution furthermore resembles that of the eosinophiles in the fact that they are relatively very scarce in the blood.

The chemical characteristics of the basophile granules is suggested by a curious phenomenon which is especially noticeable in animals, and to which Kanthack and Hardy refer in the following words: "The unstable, or *explosive, nature* of the coarsely granular basophile cells in certain animals is one of their most remarkable characters. In the rat and mouse perfect preparations of these cells may be very easily made, but in the guinea-pig and rabbit they can be preserved only with the most rapid fixation by heat or absolute alcohol. In these animals the mere exposure of the cœlomic fluid to the air, or to contact with a cover-slip for a few seconds, is sufficient to cause their complete disappearance. Cells characterized by great instability have been described elsewhere in astacus"[58] as the 'explosive' cell of that animal, and the basophile cells of the guinea-pig and rabbit might, with equal justice, be designated the explosive cells of those animals." A familiar histological fact will suggest the relationship between such a cell and adrenoxidase. Berdal,[59] quoting Ranvier, says: "The action of oxygen or of the air may be observed in an extremely simple way: A lymph preparation which has served for the examination of amœboid movements is carefully surrounded with paraffin and set aside for thirty-six hours. If, at the end of that time, the lymphatic cells are examined, all will be seen to have reassumed the spherical form and to no longer project pseudopodia. Removal of the paraffin and raising of the disk so as to admit a small quantity of air will suffice to cause the amœboid motion to recur." The explosive nature of the coarsely granular basophile cell can only be due to the one cause: the presence of large proportion of phosphorus, both in its nuclein and granules.

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[58] Hardy: Journal of Physiology, Nos. 1 and 2, vol. xiii.
[59] Berdal: *Loc. cit.*, p. 276.

In their paper upon the free granules derived from leucocytes Stokes and Wegefarth review the investigations of H. F. Müller, of Nothnagel's clinic.[87] This observer found them both in diseased and normal blood, and describes them as "highly refractive, round, or dumb-bell shaped bodies which show a dancing, molecular movement, but no independent motion." When mounted in 1 per cent. osmic acid "the reaction for fat does not occur," nor can they be dissolved by acetic acid or ether. An important feature in connection with our inquiry is that Müller is recorded as stating that "he does not consider them as Ehrlich's neutrophilic granules escaped from leucocytes," and that "the neutrophilic granules are dissolved by dilute acetic acid, while the bodies which he has studied are not dissolved by this acid." This is in perfect accord with the chemical analyses of Milroy and Malcolm, who found that acids dissolved eosinophile granules, and with the observations of Lenhartz in respect to those found in sputum. Stokes and Wegefarth further emphasize the dissimilarity of basophiles from acidophiles in general, as viewed from my standpoint, when they say, doubtless referring to Ranvier's interpretation of the purpose of the granules of white globules: "They are not concerned in the formation of fibrin, since they remain outside of the fibrinous net-work or are only accidentally attached to it." We thus have evidence to the effect that basophiles are different from neutrophiles, both chemically and functionally.

What is the nature of these granules? Müller is stated to disbelieve "that they are true particles of fat, since they do not give a reaction with osmic acid," while he is credited with the opinion "that they may be bodies resembling fat, but which fail to show the osmic acid stain." Indeed, the persistence with which this characteristic appearance is noted by investigators is noteworthy. Thus, Kölliker,[88] Ranvier,[89] Bizzorero,[90] von Lünbeck,[91] and Hayem[92] are referred to by Stokes and Wegefarth as having also observed bodies resembling fat-granules in the blood of normal human beings, those of the last-named investigator and others described by Schiefferdecker and Kossel[93] also as fat-granules being thought by Müller to be identical to those observed by him. That they are fat-*like*, as thought by Müller, but not fat, seems clear.

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[87] H. F. Müller: Centralbl. für allg. Path. u. path. Anat., vol. viii, 1896.

Müller, we have seen, refers (as do other investigators) to the fact that these granules are "highly refractive." As this sign also attends eosinophilic granules, it would appear to have but little differential value; such is not the case, however, when this property is jointly considered with the osmic acid reaction, for we have here the *two main distinctive signs of myelin*. "It is extremely refringent," writes Berdal, referring to the latter; and he also alludes to the familiar fact that "myelin treated with osmic acid" stains black.

Still, if the granules are composed of myelin, the active constituent of the latter, lecithin, should be present, since we found this body not only in the myelin of nerves, but also in that of the neuron and the interior of the dendrites. That some granules do contain this body is evident, inasmuch as Foster, in his review of the physiological chemistry of white corpuscles, writes: "Next in importance to the proteids as constant constituents of the white cells come certain fats. Among these the most conspicuous is the complex fatty body, *lecithin*." As we now know that the nuclei of all leucocytes are similar in composition, this can only apply to their granules.

This involves the necessity of differentiating between the two kinds of granules present, the acidophiles (neutrophiles and eosinophiles) and basophiles. Foster points to this distinction, it seems to me, when he says: "next in importance to the proteids," etc. The basophilic granules are evidently not composed of nucleo-proteids; a fact which eliminates the acidophile cells and their granules. Indeed, we have confirmatory evidence that it is not the latter which contain lecithin in the following allusion to both kinds of acidophile granules by Milroy and Malcolm: "The fact that neither alcohol nor ether dissolves the granules excludes the possibility that they consist of fat or lecithin."

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[88] Kölliker: "Handbuch der Gewebelehre des Menschen," 1867.
[89] Ranvier: "Traité Technique d'Histologie," 1875.
[90] Bizzorero: "Handbuch der klin. Med.," 1887.
[91] Von Lünbeck: "Grundriss einer klinischen Pathologie des Blutes," 1896.
[92] Hayem: "Du sang et de ses altérations anatomiques," 1889.
[93] Schiefferdecker and Kossel: Gewebelehre, Bd. xi, 1891.

How do basophile cells acquire their lecithin-building constituents? As is well known, emulsified fats also penetrate the intestinal villi, but, instead of entering as do nucleo-proteids into the venules, they enter the lymphatic circulation directly, by way of the lacteals. Are they absorbed by the villi, and then by the lacteals, or are they also taken up by leucocytes and carried into the latter? Inasmuch as the lymph contained in the lymphatic vessels is itself crowded with leucocytes similar to some of those found in the blood-stream, we must first ascertain whether these leucocytes in any way leave the lymphatic circulation in the intestine as they evidently do when the lymph-ducts open into the general venous system at the junction of the internal jugular and the subclavian veins on both sides.

It may prove useful, however, to recall from the start that the so-called "chyme" and "chyle" represent the same liquid, *i.e.*, the lymph, and that these terms were suggested by a temporary *quantitative* difference in the constituents of the lymph in the mesenteric lymphatics, which are greatly increased during the process of absorption. Again, it may also be well to refer to the fact that lymph is merely blood-plasma practically devoid of red corpuscles, but containing lymphocytes and coarsely granular basophile leucocytes, and, besides, minute fat-globules which show an active Brownian movement, though covered with a thin layer of protoplasm to prevent their running together as fat-drops are wont to do.

"Lymph also contains fibrin," writes Mathias Duval, "but a fibrin which is slow to coagulate spontaneously; indeed, lymph removed from the vessel begins, after a quarter of an hour or so, to harden into a colorless jelly, from which a reticulated mass soon becomes separated, as does blood-fibrin undergoing coagulation." The cause of this delay seems to me but a natural result of the absence of both varieties of acidophile leucocytes, while the slow coagulation is but a normal consequence of the fact that the lymph is plasma which, though derived from the blood, and deprived of neutrophile leucocytes, nevertheless contains more or less fibrinogen. "More or less" is applicable in a double sense here, for lymph taken from the lymphatics of the extremities, for instance, coagulates more rapidly than that taken from some vessels of the trunk. Lymph also contains serum-albumin and serum-globulin in reduced quantity, and relatively very small proportions of urea, neutral fats, and sugar, as compared to the blood. Such is not the case, however, as regards inorganic salts, which are present in the lymph and blood in similar proportions.

What is the nature of the process through which fats are taken up from the intestine and their itinerary in the blood-stream until they are used for the elaboration of basophile granules?

Stewart,[94] referring to the nature of this process, says: "The common view has long been that the greater part of the fat escapes decomposition, and, after emulsification by the soaps formed from the liberated fatty acids, is absorbed as neutral fat by the epithelial cells covering the villi. If an animal is killed during digestion of a fatty meal, these cells are found to contain globules of different sizes, which stain black with osmic acid, and dissolved out by ether, leaving vacuoles in the cell-substance, and are therefore fat. It has always been difficult to explain how droplets of emulsified fat could get into the interior of the epithelial cells, and yet it certainly passes into them, and not between them." Foster also refers to this feature in the following quotations: "It has, it is true, been maintained by some that they [the neutral fats] pass *between*[95] the cells, and not into them, but the evidence is distinctly against this view." Alluding to the rods of the striated border, he says: "We may imagine that the globules pass into the cell-substance by help, in some way, of these rods through amœboid movements comparable with the ingestive movements of the body of an amœba; but we have no positive evidence to support this view." . . . "Within the columnar cell, the fat may be seen, both in osmic acid preparations and in fresh living cells, to be disposed in globules of various sizes, some large and some small, each globule placed in a space of the protoplasmic cell-substance. It does not follow that the fat actually entered the cell exactly in the form of these *globules;* it may be that the fat passes the striated border in *very* minute spherules, which, reaching the body of the cell, run together into larger globules; but whether this is so or not we do not know."

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[94] Stewart: *Loc. cit.*, p. 370.
[95] All italics below this word are my own.

All this seems pointedly to suggest that the epithelial cells take up minute fat-particles to submit them to some local process. Böhm and von Davidoff[96] emphasize the feature of the process when they say, referring to the fat-globules in the epithelial cells: "It seemed most probable that protoplasmic threads (pseudopodia) were thrown out from each through its *cuticular* zone, which, after taking up the fat, withdrew with it again into the cell. But when it was shown that, after feeding with fatty acids or soaps, globules of fats still appeared in the epithelial cells as before, and that the chyle also contained fat, the hypothesis was suggested that the fat is split up by the pancreatic juice into glycerin and fatty acids, and that the fatty acids are then dissolved by the bile and the alkalies of the intestinal juice, only again to combine with the glycerin to form fat *within* the epithelial cells." Stewart further states that "when an animal is fed with fatty acids they are not only absorbed, but appear as neutral fats in the chyle of the thoracic duct, having combined with glycerin in the intestinal wall, and the epithelial cells contain globules of fat, just as they do when the animal is fed with neutral fat." It seems clear, from these and other available data, that *the epithelial cells of the villi capture fat-globules from the intestinal contents and if need be convert this fat into neutral fats.*

We have seen, however, that the villi also take up the leucocytes which ingest proteids. It is important, in this connection, to clearly distinguish the two mechanisms involved one from the other. Böhm and von Davidoff testify to the passage of such cells into the villi by stating: "Leucocytes are sometimes found within the epithelial cells, but more usually between them, and, according to Stöhr, when seen in these positions are in *the act* of migrating into the lumen of the intestine." Stewart, however, remarks, in this connection: "Leucocytes have been asserted to be the active agents in the absorption of fats. They have been described as pushing their way *between* the epithelial cells, fishing, as it were, for fatty particles in the juices of the intestine, and then traveling back to discharge their cargo into the lymph. This view, however, is erroneous." It is erroneous, but only in one respect, in my opinion, *i.e.*, their direct connection with the absorption of fats, for, as stated, the functions of these wandering cells is to carry proteids to the intravillous venules. These do not, therefore, enter the intravillous lacteals. But *other* leucocytes penetrate the latter with the neutral fat-globules. "Although the leucocytes do not aid in the absorption of fat from the *intestine,*" says Stewart, "they appear to take it up from the epithelial cells, conveying it through the spaces of the net-work of adenoid tissue that occupies the interior of the villus, to discharge it into the central lacteal, where it mingles with the lymph." The distinction I suggest in this connection appears to me to remove the confusion that exists in the literature of the subject. Briefly, my conception of the process is as follows: *While the leucocytes which ingest proteids from the intestinal foodstuffs pass between the epithelial cells and enter the venules, the leucocytes which ingest fats only carry the latter from the inner limits of the epithelial cells to the interior of the lacteal, and deposit them therein.*

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[96] Böhm and von Davidoff: *Loc. cit.*, p. 254.

Sir Michael Foster expresses the opinion that the number of leucocytes found to contain any appreciable degree of fat is too small to account for the amount of fat absorbed. But it seems to me that, if these only transfer the fat from the epithelial cells to the lacteals, the to-and-fro excursions of each cell and the enormous number of villi over which the food of a single meal has to pass amply compensate for the apparent paucity of cells. An additional reason adduced by Foster is the fact that the administration of a saline such as magnesium sulphate "produces effects the very reverse of absorption," these cells being present in unusual numbers. As interpreted from my standpoint, and as will be shown when the action of purgatives is studied, these agents greatly increase the flow of serum into the intestinal canal by reflex action and crowd its walls with defensive agencies, including leucocytes. We are dealing here not with a normal process, such as is the fat-absorbing function, but with an engorgement by protective elements.

The axial contraction and relaxation which occur in the villus to cause its various contents to gravitate into their respective channels may, however, be instrumental in causing fat-particles that have already passed the epithelium to enter not only the lacteal, but the venules also, fat-globules, or what purported to be such, having been found in the blood. This feature and the manner in which fat-globules reach the general lymphatic circulation are exemplified in the following lines by Stewart: "The contraction of the smooth muscular fibers of the villus and the peristaltic movements of the intestinal walls alter the capacity of the lacteal chamber, and so alternately fill it from the lymph of the adenoid reticulum and empty it into the lymphatic vessel with which it is connected. By this kind of pumping action the passage of fat and other substances into the lymphatics is aided. In the dog no fat is absorbed by the blood-vessels, except perhaps a small quantity in the form of soaps; it nearly all goes into the lacteals, and thence by the general lymph-stream through the thoracic duct into the blood."

An interesting feature now asserts itself. Again are all the basophiles poured into a channel, the left subclavian vein, which empties into a large venous trunk, the superior vena cava, which in turn carries them to the right heart. We have practically a repetition of the process witnessed in the case of the neutrophiles with the exception of the passage through the liver, the basophiles being directly transmitted to the heart, and therefore likewise to the pulmonary lobules.

Indeed, my view that the granules of these cells *are* myelin seems confirmed in this connection, for, while Lenhartz alludes to the neutrophilic granules found in colorless sputum, and to the fact that the sputum of asthmatics contains "numerous eosinophile and quite numerous *basophile* leucocytes," he also refers, when reviewing the characteristics of the cells observed microscopically in this connection, to cells that "present considerable coarse granulation," and remarks: "Here, however, the spherules show a decidedly dull appearance, resembling that seen in *crushed nerve-substances.* For this reason they were designated by Virchow as *myelin droplets.*" Moreover, Lenhartz[97] publishes a colored plate, one of the figures of which represents what he terms with E. Wagner "heart-lesion cells" found in the lungs. The granules of these, he says, "are similar to myelin, and, occasionally, *more refringent than fat.*"

Evidently the nervous system is supplied with its myelin precisely as the muscles are supplied with their myosinogen. Kanthack and Hardy state that the coarsely granular cells are not only rare, but completely absent from the blood, while the finely granular are relatively rare in the latter except some hours after a meal. "To say that these cells are found in the body only in very small numbers, being confined to the blood and scanty even there," remark these investigators, referring to the finely granular basophiles, "is probably only equivalent to saying that we are at present very ignorant as to their history, distribution, and significance. However, since we find this cell in the blood, but do not find it either in the cœlomic fluid or in the interstitial spaces of the tissues (except, perhaps, in those of the mucous coat of the *alimentary canal*), we must, until further facts are forthcoming, regard it as the basophile cell of the blood." Still, they refer to the coarsely granular cells as "occurring only in the extravascular spaces" and in the "interstices of the connective tissue."

It is probable that we have in the finely granular cell the freshly laden cell on its way, when in the blood, to its normal habitat, the connective-tissue spaces, where their granules develop into their normal size. Indeed, Gulland alludes to a basophile cell, represented in one of his plates, of which he says: "The leucocyte was seen to have been fixed in the act of *passing through a narrow hole* between two bundles of connective tissue." This cell is furthermore accompanied by a large number of granules held in a net-work of fibers, which the cell appears to drag along in its travels. It is of this variety of leucocyte that Gulland says: "It has often been remarked that these cells show a great tendency to leave their granules behind them," etc., and the one which, in the portion of this section devoted to a review of the general properties of leucocytes, stands pre-eminently as a free-granule producer.

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[97] Lenhartz: "Mikroskopie und Chemie am Krankenbett." 1900.

That the cell in migrating from the vessels and passing through connective-tissue interstices has for its purpose to reach the myelin-spaces of nerves is clearly suggested by the manner in which the lymphatic spaces are arranged even in the finer ramifications. "In its course Henle's sheath is not applied against the nerve-tube," writes Berdal[oo]; "there is between it and the nerve-tube a space occupied by lymph-plasma which has for its purpose to supply the cylinder-axis with its nutrition." If this statement is interpreted from the standpoint of my views, it is more than nutrition, but myelin-granules, which insinuate themselves—through chemical affinity, doubtless—wherever there is need for them: *i.e.*, wherever their consumption has been greatest. "Medullated nerve-fibers, when examined, frequently present a beaded or varicose appearance," say Pick and Howden[pp]; "this is due to manipulation and pressure causing the *oily* matter to collect into drops, and in consequence of the extreme delicacy of the primitive sheath even slight pressure will cause the transudation of fatty matter, which collects in drops of *oil* outside the membrane." Evidently we are not dealing with a fixed mass, but with one made up of extremely mobile particles, which to me, at least, represent as many basophile granules. If the space between Henle's sheath contains lymph supplied with myelin-granules, what is the difference between a nerve thus supplied with its primary source of energy and a "medullated" nerve? None, in my opinion. *Such a nerve as a non-medullated nerve does not exist,* therefore, since a nerve deprived of myelin, if interpreted from my viewpoint, would become a mere plasma-channel.

The pathway to all nerves becomes greatly simplified down to their terminal ramifications, it seems to me, in the presence of Gulland's observation concerning the passage of a basophile leucocyte "through a narrow hole between two bundles of connective tissue." Indeed, "the lymphatic vessels do not exist as distinct channels in the interfascicular connective tissue," says Berdal. "There is no lymphatic vessel in the thickness of the nervous bundles nor in the sheath surrounding them (Ranvier). The circulation of the lymph in the interior of the bundles is insured by the arrangement of the interfascicular connective tissue, the meshes of which represent lymphatic cavities communicating with the vessels of the interfascicular tissue through *holes* in the lamellar sheaths." On the whole, therefore, it seems to me permissible to conclude that:—

[oo] Berdal: *Loc. cit.*, p. 152.

[pp] Pick and Howden: *Loc. cit.*, p. 1112.

1. *The physiological function of the basophile leucocyte is to convert fats derived from the intestinal foodstuffs into myelin-granules, and to distribute the latter to all parts of the nervous system, including the brain.*

2. *The basophile leucocytes thus supply the entire nervous system with the lecithin-containing compound which combines with the adrenoxidase of the blood-plasma of axis-cylinders, neuroglia fibrils, etc., in the production of nervous energy.*

The different varieties of leucocytes reviewed so far represent, it seems to me, the only three *adult* functional types, the lymphocytes and hyalines being, as stated, immature cells. This does not mean, however, that the latter are functionless; indeed, we have seen that when an active process is initiated these younger cells rapidly increase in the blood and intestinal tract, to replace the large number of their elders that have disappeared to take part in this process. Their development must be extremely rapid, therefore, and their number commensurate with the number of adult leucocytes brought into action, whether this be to distribute (1) the neutrophilic peptones, myosinogen- and fibrinogen- granules, (2) the eosinophilic hæmoglobin granules or (3) the basophilic myelin-granules.

THE FUNCTIONS OF THE LEUCOCYTES IN IMMUNITY.

As the study of the functions of these cells is continued and amplified in the second volume, I will merely incorporate in this section a few brief facts based on the data submitted in the foregoing pages and conclusions based on a study of the subject, which study cannot for want of space be reproduced here.

Metchnikoff terms "phagocyte" any cell deprived of a cellular membrane and capable of incorporating bacteria and other substances, and of disintegrating them. In the blood, certain leucocytes, particularly the mobile or wandering neutrophilic or polymorphonuclear forms (the "microphages"), the fixed endothelial and connective-tissue cells, those of the splenic pulp, and the large lymphocytes of the blood ("macrophages") are endowed with this property. Precisely as do the familiar amœbæ, so do these phagocytes ingest bacteria and assimilate them. An

EXPLANATION OF PLATE.—Fig. 1.—Pfeiffer's phenomenon occurring in the exudation taken from an untouched guinea-pig, the exudation having been withdrawn ten minutes after the injection of 1 cubic centimeter of bouillon containing one loopful of a culture of Constantinople cholera and 0.04 cubic centimeter of preventive serum (of the strength of $^1/_5$ milligramme). Staining with methylene-blue. *l*, Lymphocytes. Ocular 3. $^1/_{12}$ Zeiss.

Fig. 2.—Mass of granules placed around a collection of leucocytes. Exudation of a guinea-pig withdrawn nine minutes after the injection of 1 cubic centimeter of bouillon to which had been added a third of a culture of Oriental-Prussia cholera and 0.04 cubic centimeter of preventive cholera serum of goat (strength, 0.0002). Ocular 2. D. Zeiss.

Fig. 3.—Granular leucocyte surrounded by a zone of vibrionic granules. The exudation was withdrawn twenty-five minutes after the peritoneal injection of one-tenth of an agar-agar culture of Massowah vibrio. Ocular 2. $^1/_{12}$ Zeiss.

Fig. 4.—Two mononuclear leucocytes surrounded by granules; a lymphocyte (*l*) and a red blood-corpuscle (*h*) from the same exudation. Same power.

Fig. 5.—The same cells after remaining for three and one-half hours at 37°.

Fig. 6.—Five polynuclear leucocytes from the exudation withdrawn four minutes after the injection into the peritoneum of a guinea-pig (highly vaccinated and prepared with 3 cubic centimeters of bouillon) of 1 cubic centimeter of bouillon with one-third of an agar-agar culture of Oriental-Prussia cholera. *n*, Nucleus of a crushed macrophage. Staining with methylene-blue. Ocular 2. $^1/_{12}$ Zeiss.

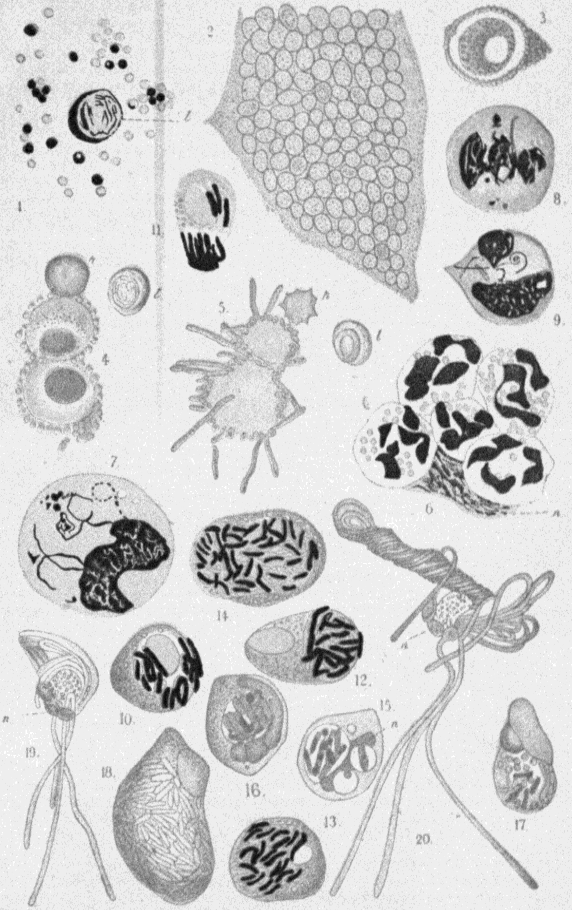
Fig. 7.—Mononuclear leucocyte filled with Courbevoie cholera vibrios. Peritoneal exudation of a guinea-pig. Ocular 3. $^1/_{12}$ Zeiss.

Figs. 8 and 9.—Two polynuclear leucocytes from the same exudation. The vibrios stained gray in the plate are vibrios in the eosinophile stage. Ocular 3. $^1/_{12}$ Zeiss.

Figs. 10 to 14.—Various phases in the formation of cultures of cholera vibrio (Oriental Prussia) within leucocytes. Hanging drop, stained with methylene-blue, of the exudation of a guinea-pig hypervaccinated for almost six months and prepared with 3 cubic centimeters of bouillon. The exudation was withdrawn four minutes after the peritoneal injection of one-third of an agar-agar cholera culture placed in 1 cubic centimeter of bouillon and kept at 36°. Ocular 3. $^1/_{12}$ Zeiss.

Figs. 15 to 18.—Various phases in the formation of cultures of the Kiel red bacillus within leucocytes. The hanging drop was kept for twenty hours at 17° and was made with the exudation from an hypervaccinated guinea-pig prepared with an injection of 3 cubic centimeters of bouillon. The exudation was withdrawn four minutes after the introduction into the peritoneum of the Kiel bacilli. Ocular 2. $^1/_{12}$ Zeiss.

Figs. 19 and 20.—Two consecutive phases of a culture of Kiel red bacilli grown from within a polynuclear leucocyte in a hanging drop of peritoneal exudation. The drop was prepared from the exudation of an hypervaccinated guinea-pig, withdrawn three hours and fifty minutes after the injection of Kiel bacilli into the peritoneum. *n*, Nucleus. Ocular 2. $^1/_{12}$ Zeiss.



INTRAPHAGOCYTIC DESTRUCTION OF BACTERIA. *[Metchnikoff.]*

[*Annales de l'Institut Pasteur.*]

animal is immune, according to Metchnikoff, as long as its phagocytes freely take up and destroy pathogenic organisms. In proportion, on the other hand, as the functions of the phagocytes are impeded, so is the animal susceptible to disease. That living and dead bacteria are thus disposed of seems to have been satisfactorily shown, while chemotaxis fairly accounts for the affinity which phagocytes show for certain germs in preference to others. Metchnikoff's doctrine as regards the power of certain leucocytes, migrating and fixed, to act as phagocytes is sustained by experimental evidence; the process can easily be followed visually and the leucocytes be seen to ingest micro-organisms, to which they are drawn by chemotactic influence. In 1862 Haeckel witnessed the ingestion of indigo by leucocytes; in 1863 Recklinghausen observed that pus-cells were endowed with amœboid motion, and, having injected cinnabar grains in the dorsal lymph-sac of frogs, saw that they were ingulfed by cells floating in the lymph.

Cohnheim, as long ago as 1867, noted that the smaller vessels of the mesentery became dilated and saw leucocytes range themselves along the vascular walls, plunge their pseudopodia through the mural stomata, and penetrate beyond them, thus migrating and becoming "pus-cells." These pus-cells, in the light of Metchnikoff's theory, are the remains of protective microphages which have succumbed after migrating through vascular walls to meet offensively the pathogenic organism. Dead material, pigment-granules, fragments of tissue, dust-particles, indigo, ivory (in the osseous medullary canal, according to Kölliker), in fact, almost any foreign substance capable of invading the living organic structure, seems to become their prey. An aseptic catgut ligature, a fragment of bacilli-laden tissue, etc., soon becomes coated with an exudate filled with leucocytes which first ingulf the bacilli and then the disintegrated tissue. Let any inhibiting cause appear, however,—an excessively virulent germ, an abnormally high temperature, for instance,—their powers cease, and at once the bacilli multiply, causing death of the animal used for the experiment. The rapidity of multiplication of pathogenic organisms is an additional factor operating against successful phagocytic action. When such is the case the phagocytes are themselves destroyed.

Successful phagocytes may be traced from their working field by staining the latter, as was done by Rosenberger; long lines of colored cells may then be seen to radiate in various directions from the stained area. The pathogenic germs, once ingulfed, usually cease to multiply, and, either through a toxic action or starvation, soon die and disappear. That organisms are ingested alive Metchnikoff has shown. Spermatozoa, for instance, ingested by macrophages were seen to continue their motile activity until the tail had also been taken up. Begun in 1865 with the digestive epithelium of *Gedesmus bilineatus,* the cellular elements of which were shown to digest various extrinsic substances, Metchnikoff's labors developed in 1883 into his present doctrine of phagocytosis, which, notwithstanding much adverse criticism, has maintained its ground.

The rapidity with which the protective process is carried on in cases of general infection is well illustrated by Cantacuzene:[100] "Immediately after injecting anthrax bacteria in a vein of a rabbit's ear," says this author, "the organisms are taken up by phagocytes. At the end of seven minutes in the liver, eight minutes in the lungs, and one hour in the spleen none of the germs are free. Their destruction in the phagocytes is at first very rapid, but soon some of the latter are overcome, and the bacteria, by multiplying within them, cause them to become centers of pullulation. Still, the bacteria that escape from the dead phagocyte are seized by others; but, the number of the former becoming greater as the battle progresses, their protective powers are correspondingly reduced, and the bacteria finally invade the entire blood-stream. In the liver . . . practically all the bacteria are destroyed and digested within a few minutes after the injection. This superiority of the hepatic phagocytes in the fray lasts almost throughout the disease; but the activity of the phagocytes finally decreases; the bacteria multiply within them and become generalized. In the lungs there is rapid destruction of bacteria by polynuclear cells, then intracellular development of bacteria and generalization."

The phagocytes just referred to, the microphages, are wandering or migrating cells—free to respond and travel more or less promptly toward pathogenic bacteria, in virtue of the chemotactic attraction possessed by the latter. The process is graphically illustrated in the annexed colored plate.

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[100] Cantacuzene: Quoted by Marcel Monnier: Gazette médicale Belge, July 13, 1899.

What is the nature of the intraphagocytic process?

I have shown that the germicidal phagocytes, the neutrophiles, absorbed trypsin not only in the intestinal canal while ingulfing foodstuffs, but likewise in the portal vein, the ferment in the latter being, from my viewpoint, the splenopancreatic secretion. This intraphagocytic trypsin is capable of digesting not only certain poisons: toxic albuminoids, toxins, vegetable poisons, venoms, and even drugs, as will be shown in the second volume, but also bacteria. In other words, all materials, poisons, germs, etc., find their doom in the digestive vacuoles of the phagocyte. "Just as amœbæ digest their prey with the aid of amibodiastase, a soluble ferment belonging to the group of the trypsins," writes Metchnikoff, "white corpuscles submit the foreign bodies they inglobe to the action of cytases. These cytases (the alexins or *complements* of other authors) are the soluble ferments which also belong to the category of *trypsins*."[101] The two italicized[102] words should be carefully noted, as they indicate that the antibody Ehrlich has termed "complement" is Metchnikoff's "trypsin." As shown in the second volume, this is confirmed from various directions.

As to the rôle of this cytase or trypsin-like body, it is also clearly defined in another sentence by Metchnikoff: "In blood removed from the body the white cells allow plasmase, which causes coagulation of fibrin and the formation of the clot, to pass into the liquid. But at the same time these abandon a portion of their cytase, which communicates to the serum its *hæmolytic* and *bactericidal* qualities." Briefly, when bacteria are ingested by phagocytes or phagocytic cells of any kind (for these include the finely granular oxyphiles and the hyaline and giant cells, all wandering cells) they are actually digested in their vacuoles by the trypsin-like cytase precisely as they would be in the alimentary canal of highly organized animals.

It becomes a question now as to *how* the phagocytes become supplied with this trypsin, and how their protective activity to the system at large is awakened. Considered from my viewpoint, *i.e.*, with the structure and functions of leucocytes, as described in the foregoing sections, those cells which are phagocytic are influenced in the following manner, when pathogenic bacteria, their toxins, toxic albuminoids, etc., provoke an autoprotective reaction in the body:—

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[101] L'Immunité dans les Maladies Infectieuses, p. 573, 1901. See vol. II, p. 997, for additional evidence.

[102] The italics are my own.

Stimulation of the adrenothyroid center by the toxic increases the production of adrenoxidase and thyroiodase, which in turn enhance correspondingly oxidation and, thereby, the functional activity of all tissues. Among these tissues are (1) those which produce phagocytes (lymphatic structures mainly), thus causing leucocytosis, and also (2) the spleen and pancreas, which jointly (from my viewpoint) produce Metchnikoff's trypsin-like cytase (Ehrlich's complement). This substance, being secreted (as an internal secretion, see p. 367) into the splenic and portal veins, is taken up therein by the newly created phagocytes and stored in their perinuclear vacuole,—their stomach, so to say. The cells, after traversing the liver, penetrate into the general circulation and carry on therein their function of scavengers, *i.e.*, that of ingesting and digesting the pathogenic substance or the bacteria whose toxin had excited the adrenothyroid center—the sentinel whose mission was to start the defensive reaction.

How Bacterins (Vaccines) Act and how Opsonins Enhance Phagocytosis.—We have seen that in 1907 I advanced the view that the thyroparathyroid secretion corresponded in its chemical, physiological, and clinical properties with Wright's opsonins, and that the labors of Marbé, Malvoz, and Stepanoff have sustained me. I have also submitted evidence to the effect that it was by increasing the sensitiveness of the *phosphorus* of all cells, and particularly their nuclei, to the oxidizing action of the adrenoxidase that functional activity was enhanced. We have now seen that leucocytes, including the phagocytes, are supplied, like other cells, with a nucleus rich in phosphorus. When, therefore, an excess of thyroparathyroid secretion, *i.e.*, opsonin, appears in the blood, through the above-described mechanism, and through the red corpuscles, the phagocytes become unusually active and aggressive.

Simultaneously, the pathogenic organisms themselves undergo a process which renders them vulnerable to the phagocytic host. The thyroparathyroid secretion, we have seen, powerfully excites metabolism, but particularly the catabolic phase of the process; hence its potent action in the reduction of obesity; it influences bacteria precisely as it does adipose tissue, and with especial activity those that are rich in phosphorus, the tubercle bacillus, for example. It renders the germ more vulnerable to digestion by the trypsin of the phagocyte. This effect on them modifies the surface of the germs, softens it and causes them to adhere together, *i.e.*, to agglutinate.

This suggests that opsonin and *agglutinin* are one and the same thing. That such is the case is shown by many experimental facts. We have seen that the thyroparathyroid secretion, which is the opsonin, and the adrenoxidase are contained in the red corpuscles; Nolf[103] noted that the addition of red corpuscles to serum gave it agglutinating properties. Indeed, Arthur Klein[104] found that agglutinin could be dissolved out of the red corpuscles by means of salt solution or distilled water. It will be recalled that I traced the thyroparathyroid secretion, *i.e.*, the opsonin, to the lungs; Ruffer and Crendiropoulo,[105] in a study of agglutinins, remark: "Strangely enough the lungs of immunized guinea-pigs were the only organs which in the majority of cases possessed agglutinating properties greater than the serum." As is well known, Bordet's "sensibilisatrice" is derived from the red corpuscles; now, Savtchenko[106] has pointed out that this substance was endowed with specific opsonic properties, acting both on bacteria and on leucocytes, as I explained above. Finally, agglutination is evidently a feature of opsonins. Bulloch and Atkins,[107] for example, were led experimentally to conclude that opsonins were "simple substances resembling agglutinins."

This involves the necessity on the part of the opsonin of leaving the red corpuscle to influence morbidly the bacteria. Nolf[108] showed that this was due to an action of the complement (the phagocytic trypsic cytase) on the red corpuscles which caused "the contents of the latter to leave them," and that "the injection of the corpuscular contents incited hæmolysis." In other words, the trypsin of the phagocytes being secreted into the blood, it causes the red corpuscles to secrete their opsonin (with the adrenoxidase—amboceptor), and digestion entailing destruction of the germ can thus occur in the plasma and prove so active, in fact, when there is hyperpyrexia, for example, as to destroy the blood-cells besides, *i.e.*, produce hæmolysis.

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[103] Nolf: Ann. de l'Inst. Pasteur, xiv, p. 297, 1900.
[104] Arthur Klein: Wiener klin. Woch., Apr. 17, 1902.
[105] Ruffer and Crendiropoulo: British Medical Journal, Apr. 5, 1902.
[106] Savtchenko: Annales de l'Inst. Pasteur, xvi, p. 106, 1902.
[107] Bulloch and Atkins: Proc. Royal Soc. of London, lxxiv, p. 379.
[108] Nolf: Annales de l'Inst. Pasteur, xiv, pp. 297, 492, 1900.

The bacteria being softened by the opsonin and rendered more inert, while simultaneously the phagocytes, their enemies, are rendered more active and aggressive, the former are attacked and ingested and they are submitted to digestion in the phagocytic vacuole and destroyed.

On the whole, as viewed from my standpoint, the functions of the leucocytes in general immunity, including Metchnikoff's conception of phagocytosis, may be summarized as follows:—

1. When bacteria appear in the blood, their toxins—or bacterins or vaccines injected into the tissues which ultimately reach the blood—awaken a defensive reaction in the body at large by exciting the thyro-adrenal center, oxidation and metabolism being increased in all tissues, the production of phagocytes is activated and their aggressiveness is intensified.

2. The thyroparathyroid secretion (opsonin and agglutinin) and the adrenoxidase (amboceptor) stored in the red corpuscles are then secreted by these cells under the influence of the phagocytes (Nolf), to sensitize and soften the bacteria.

3. The bacteria are then ingested by the phagocytes and digested by their cytase (complement), a trypsin-like ferment, and this process continues as long as there are bacteria to produce toxins capable of exciting the adrenothyroid center.

This completes the process as far as the phagocytes are concerned. As their functions are to co-operate with the plasmatic defensive process described under the preceding heading, the nature of this co-operation should also be ascertained. This is described in what I believe to be:—

A SIMPLIFIED THEORY OF IMMUNITY.

There occurs, at first, what might be termed the "preparatory" stage, the purpose of which is to increase the defensive constituents of the blood and other body fluids. On the whole, it seems permissible to conclude that:—

The toxic (certain toxins, wastes, drugs, vaccines, etc.) excites the immunizing center. This center, in turn, stimulates the thyroparathyroid glands and adrenals, thus causing them to supply the blood (and to a certain extent the lymph and serous fluids) with an excess of THYROIODASE *and* ADRENOXIDASE. *Metabolism being enhanced in all tissues by these substances, the pancreas also secretes an excess of* TRYPSIC FERMENT, *while the leucocytogenic tissues (bone-marrow, lymph-glands, etc.) produce an increased number of leucocytes, mainly* FINELY GRANULAR OXYPHILES *and* PHAGOCYTES.

The blood and other body fluids being now provided with all its defensive agents, the following process is started:—

The thyroiodase (opsonin, agglutinin) sensitizes and softens the pathogenic agent, while the adrenoxidase (amboceptor) oxidizes the phosphorus of the nucleo-proteid granulations, liberating heat; the activity of the trypsic ferments (plasmatic and phagocytic complement) being correspondingly increased the pathogenic agent is converted into benign and eliminable products.*

The whole process imposes protective properties upon each ductless gland involved, *i.e.*, the thyroparathyroid apparatus, the adrenals and the pituitary. As to the two first named their power to antagonize intoxication is now generally recognized. As to the pituitary body, its rôle in this connection has only, so far, been studied by myself. Suggestive, however, are the remarks of J. A. Flexner,[109] in reference to the after effects of removal of the pituitary for tumor of this organ. "I wish to call attention," writes this observer, "to the extreme susceptibility of these patients to morphine and to autointoxication, especially of purin origin." Then, referring to a personal fatal case, he states that "one twenty-fourth of a grain kept her narcotized for over a day," and he rightly concludes that "this sudden and unexpected end was due to stopping of her glandular feedings and to the severe autointoxication which resulted from her careless dietary." The rôle I have ascribed to the pituitary body alone explains this phenomenon.

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* This relationship of the nucleo-proteid granulations with functional efficiency of the cytase is studied in the second volume, to which the reader is referred.

[109] Flexner: Louisville Monthly Journal of Medicine and Surgery, May, 1912.

CHAPTER XII.

THE INTERNAL SECRETIONS AND ORGANOTHERAPY.

THE FUNDAMENTAL PRINCIPLE OF THE ACTION OF ORGANIC PREPARATIONS.

AMERICAN textbooks afford no clue as to the manner in which the thyroid gland carries on its functions. Some writers hold that the thyroid and parathyroids, by means of an internal secretion, "exercise an important control over the processes of nutrition of the body"; others contend that the purpose of these organs "is to neutralize or destroy toxic substances formed in the metabolism of the rest of the body." Others again assert that it increases metabolic activity, especially catabolism. I have submitted ample evidence to the effect that the thyroid influences all these functions; but *how* does it do so? This is the feature that I have supplied in the present work. If the reader will take into account the fact that the above divers functions, attributed by different groups of investigators to the thyroid, are *all* explained by the one rôle I have attributed to this organ—that of sensitizing the organic phosphorus of all tissues—he will surely concede that my position must be a strong one. And this may be said to apply to the other organs analyzed in this work. The analyses I have submitted have not been destructive; they have proven constructive; they have shown that different sets of experiments and clinical observations which apparently divided several groups of investigators upon each question into as many antagonistic camps were all, when interpreted from my viewpoint, conciliated and harmonized into a consistent whole.

In their application to organotherapy, my views are submitted to a still greater test: they are shown to explain *all* the therapeutic effects of preparations of the organs studied in the present work, namely, the thyroid, parathyroids, adrenals, pituitary, pancreas, spleen, and thymus. Certain organs, such as the kidneys, ovaries, and testicles, whose internal secretions have been specifically studied, may now be included in the list, for there is good ground for the proposition, at least, that their organic products should not be regarded as special secretions, but as the product of a single kind of secretory cells that are common to many organs, the adrenal cells.

If our object to place pharmacology on a scientific footing is ever to be realized, we should insist, whenever an agent is to be tried therapeutically, upon a preliminary determination of its identity as a chemical body. Thus only will it be possible for us to establish its physiological action on a solid basis. In drug therapy, this important feature has been carried out to a considerable extent, and what we know of the physiological action of most agents derived from plant life has been acquired since their active principles have been isolated and made the basis of experimental and clinical study. Just as opium contains various principles—morphine, apomorphine, codeine, etc.—so do animal extracts contain a multiplicity of substances, cellular and plasmatic, and also products of cellular metabolism capable of provoking physiological effects; but here very little effort has been made to isolate the truly useful principles. Hence the confusion and empiricism which has always surrounded the use of these agents.

All this applies to organotherapy as it does to pharmacal agents. It is unquestionably true that we have among the twenty and odd animal extracts that have been proposed a few, at least, which are capable of affording relief where no other class of agent will act—thyroid preparations in myxœdema and cretinism, and adrenal extractives in Addison's disease and hæmorrhage, for example. The adoption of a systematic line of study in the direction proposed seems to me to facilitate the discovery of additional useful applications of these agents, or, at least, to give their use in practice a more rational basis.

Important in this connection is the identification of the true organotherapeutic preparations. By the "true" agents I mean those which can be used intelligently, that is, with knowledge of the physiological effects produced, because their active principles are known. Thyroid extract belongs to this class, since we know that its action is due to the iodine in organic combination its secretion contains; adrenal preparations likewise are included because their active principles, whether epinephrin, suprarenalin or adrenalin, are also known. Conversely, we have a large number of organic preparations that are used blindly, without knowledge of their components, which may number from five to twenty or more, in almost any disease related directly or remotely with the organ from which the extract is obtained. Mammary extract can be cited as an example of these agents. They are hardly entitled to a rank much above that of empirical nostrums until rendered fit, by their sponsors, through chemical, pharmacological, and clinical researches, to be taken up by the profession as legitimate pharmaceutical agents.

That so desirable a task is not impossible of accomplishment may readily be shown. We shall take as examples those which, besides the thyroid, parathyroid, and adrenal products, whose active agents are familiar to every one, the four which have stood out most prominently in the history of opotherapy: the testicular, ovarian, renal, and pituitary extracts.

Spermin, as is well known, is the purest of testicular preparations. Before I had given any attention whatever to these agents, I had submitted evidence[1] which showed that the adrenal secretion was carried to the pulmonary air-cells, to take up the oxygen of the air therein, and become the albuminous (previously unidentified) constituent of the hæmoglobin, which, through the intermediary of the red corpuscles, supplies oxygen to all the tissues. The evidence showed that it was an oxidizing body acting catalytically; that it resisted all temperatures up to, and even, boiling; that it was insoluble in ether and practically insoluble in absolute alcohol, and gave the guaiac, Florence, and other hæmin tests. Now, spermin not only raises the blood-pressure, slows the heart, and produces all other physiological effects peculiar to the adrenal principles, but its solubilities are the same; it gives the same tests; it resists boiling. Moreover, it is regarded in Europe as a powerful "oxidizing tonic" and has been found equally useful in disorders in which adrenal preparations had given good results. The inference that spermin consists mainly of the adrenal product suggests that it should not be regarded as specific to the testes, but, instead, a constituent of the blood at large; not only did this prove to be the case, but it was found in the blood of females as well as in that of males, as we have seen.

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[1] Sajous: "Internal Secretions and the Principles of Medicine," i, 1903; ii, 1907.

As I have also shown in a previous chapter, the dependence of ovarian preparations, including corpus luteum, upon the adrenal principle for their activity is no less evident. Ovarian extract has been found to contain "an oxidizing ferment comparable to spermin."[2] Just as castration causes a decline of the temperature, so does removal of the ovaries; while both spermin and ovarin restore the temperature to normal. This corresponds with the influence on general oxidation I ascribe to the adrenal secretion. As is the case with the latter, ovarian preparations enhance metabolism and the excretion of phosphoric acid. Again, the resemblance of the effects of ovarian preparations to those of adrenal gland is striking. "Fresh ovarian extract," writes Wilcox,[3] "is said, when injected in rabbits, to raise the blood-pressure, diminish the heart's action, and slow the respiration; and when administered to the human female, also to increase the arterial tension. In the castrated animal it is found to increase oxidation to something above the normal degree." Sauvé[3a] states that it increases oxidation and the proportion of hæmoglobin in the blood.

Besides this mutual relationship between the testicular, ovarian and adrenal products, two suggestive facts assert themselves: Not only have Schäfer and others found that a close analogy exists between the interstitial cells of the testicles and ovaries and the cells of the adrenals, but all three sets of organs are derived from the Wolffian body.

The kidneys have been credited with an internal secretion, but no experimental work so far recorded justifies such a conclusion. There is, however (see page 467), testimony to the effect that, as in the organs just referred to, the adrenal principle is the main active agent. Batty Shaw,[4] remarking that the favorable effects obtained from renal extracts are similar to those that "have been reported as a result of treatment by means of spermin and testicular extract," suggests that "possibly nephrin and other renal preparations provide a means of stimulating oxidation in general, the kidney merely sharing in this oxidation." The concordance of this opinion with my own view (1903), that the adrenal secretion is the constituent of the hæmoglobin molecule which carries on oxidation, is self-evident. The influence of renal extracts on oxidation is further shown by the observations of Brown-Séquard, Teissier, and Fränkel,[5] that they increased the output of urea, phosphates, and uric acid, and by those of Brown-Séquard, Dromain, and de Pradel Bra,[6] Mois,[7] Bitzou,[8] Dubois,[9] and others, which showed that they possessed marked antitoxic power. This also harmonizes with my views, since I have shown, with ample evidence to sustain this assertion, that the adrenal secretion is a basal factor in *all* immunizing processes—as its rôle in oxidation would normally suggest. Even the morbid effects of exaggerated antitoxic activity which I ascribed to excessive doses are exemplified by an observation of Layral's[10] in which renal extract caused death from pernicious anæmia, *i.e.*, from hæmolysis.

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[2] Batty Shaw: "Organotherapy," 1905.

[3] Wilcox: "Pharmacology and Therapeutics," 7th ed., p. 824, 1907.

[3a] Sauvé: Paris médical, April 1, 1911.

[4] Batty Shaw: *Loc. cit.*, p. 216, 1905.

Pituitary extracts, we have seen, are active according to which of the two lobes of the pituitary is used to prepare them. Howell, Silvestri, Thaon, and others have found that extracts of the anterior lobe were practically inert, while those of the posterior proved quite active. Howell[11] states in this connection that they "cause a marked rise of blood-pressure and slowing of the heart-beat," remarking, moreover, that "these effects resemble in general those obtained from adrenal extracts, but differ in some details." When we take into account the wealth of this organ in nervous elements, deviations in minor effects are readily accounted for.

As previously stated, the adrenal principle is not destroyed by boiling. This was also observed to be the case with extracts of the pituitary lobe, by Schäfer and Herring.[12] These physiologists also noted that they produced dilatation of the renal vessels, but this is a normal result of the vasoconstriction produced by them in the body at large, owing to the action of the adrenal principle upon the vascular muscles. The renal capillaries, in keeping with all others, being deprived of muscular elements, they are passively dilated by the blood compressed out, as it were, of the larger vessels and the kidneys are dilated.

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[5] Teissier and Frankel: Lyon médical, April 29, 1894.
[6] Bra: Comptes-rendus de la Société de Biologie, July 26, 1895.
[7] Mois: Clinica Moderna, Dec. 1, 1897.
[8] Bitzou: Journal de physiologie et de pathologie générale, Nov. 15, 1901.
[9] Dubois: Bulletin général de thérapeutique médicale et chirurgicale.
[10] Layral: Bulletin médical, Oct. 8, 1898.
[11] Howell: *Loc. cit.*, 2d ed., p. 802, 1907.
[12] Schäfer and Herring: Transactions of the Royal Society, cxcix, p. 1, 1906.

Herring,[13] and more recently McCord,[13a] noted that pituitary extract caused constriction of the peripheral arterioles. This is typical, as is well known, of the action of all adrenal products. As shown by the experiments of Garnier and Thaon,[14] Conti and Curti,[15] and others, the pressor precede the depressor effects. This applies as well to the inhibitory effects on the pancreas recently recorded by Pemberton and Sweet.[16] The mydriatic action of epinephrin, discovered by Meltzer, has also been found by Cramer to apply to pituitary extract. Finally, the clinical effects recorded, especially those on the cardiac disorders by Cyon, Rénon and Delille,[17] clearly indicate that they are due to the adrenal principle pituitary extracts contain. Both are extolled as oxytocics, being deemed far superior to ergot by some. Both also have been found very effective in intestinal paresis. The resemblance of their action to that of adrenal extracts, noted by Schäfer, is explained, therefore; it is to the adrenal principle in the pituitary that extracts of this organ owe their activity. Finally, as shown by Wiesel,[18] the pituitary body is the seat of a large group of chromaffin cells, *i.e.*, adrenal cells. Watanabe and Crawford[18a] then found that pituitary extracts contained "an epinephrin-like compound.

All the facts seem to me to justify the inclusion of testicular, ovarian, renal, and pituitary extracts in the adrenal group of organic extracts.

I would add that the presence of the adrenal principle throughout the organism is no longer to be doubted. Besides its now-familiar effects on the blood-pressure by a direct action on the blood-vessels, which necessitates its distribution broadcast, we have the fact that Mulon found it in the red corpuscles. Even the placental blood contains it. As a conservative pharmacologist, Dixon,[10] wrote, while describing investigations by F. Taylor and himself: "We have shown that the human placenta contains a considerable amount of a substance which is . . . unaffected by boiling. This body has the property of powerfully constricting blood-vessels, of contracting the uterine muscle, of raising the blood-pressure. . . . So far as we have been able to determine, this body has all the properties of adrenalin." Indeed, "adrenalinemia" is now in common use.

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[13] Herring: Journal of Physiology, Nov. 2, 1904.
[13a] McCord: Archives of Int. Med., Nov. 15, 1911.
[14] Garnier and Thaon: Jour. de phys. et de path. gén., March, 1906.
[15] Conti and Curti: Bollettino delle scienze medicale, Nov., 1906.
[16] Pemberton and Sweet: Archives of Internal Medicine, July, 1908.
[17] Rénon and Delille: Journal des praticiens, No. 42, 1907.
[18] Wiesel: International Clinics, vol. ii, 15th series, 1905.
[18a] Watanabe and Crawford: Jour. of Pharmacol. and Exp. Ther., Jan., 1916.

The adrenal principle being common to the entire organism, it would seem as if all organic extracts should owe their therapeutic activity to this constituent. But many facts go to show that the proportion of adrenal principle in certain organs—those forming part of the chromaffin system, for example—is far greater than in others, and moreover that they contain cellular elements that are not only similar to the secreting elements of the adrenals, but which are capable of adding to that received from the latter through the blood. This accounts for the fact that removal of the testicles or ovaries lowers the activity of the oxidation processes, though without destroying life itself, as is the case when the adrenals are removed. The obesity which follows removal of the testicles or the ovaries illustrates an effect of this suboxidation.

This does not mean, however, that all organic preparations owe what therapeutic efficiency they have shown mainly to the adrenal principle they contain. The majority of them probably do not. The recent introduction of an oily extract of brain matter seems to have placed the use of this agent on a firmer basis. The phosphorus-laden nucleins derived from brain substance would probably account for what therapeutic value it seems to show. Again, thymus extract has some claim to recognition in disorders which other remedies do not seem to affect. Here again, we have a tissue rich in nuclein, and therefore in phosphorus. May we not have in these and other organic preparations a means of introducing into the body phosphorus so bound up in organic combination that it can be far more readily taken up by our tissues than any preparation that our laboratories can produce? We must not lose sight of the fact that organotherapy affords, precisely in this direction, possibilities that nothing else in the realm of therapeutics can offer—a statement which applies also to the opportunity they furnish of introducing immunizing bodies directly into the blood—or of compensating for organs whose functions have become inadequate through local disease. But these advantages will only become available when the prevailing empirical use of animal extracts will have been rendered impossible through proper identification of those of their constituents which bring about beneficial effects, the natural precursor to a clear conception of their mode of action.

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[10] Dixon: British Medical Journal, Sept. 21, 1907.

Another important feature is the distinction of true ductless glands, whose mission is to elaborate a secretion of physiological use to the body at large, from organs which have been credited with such functions on insufficient grounds. Perhaps the habit of requiring considerable evidence from many sources and directions before reaching a conclusion—contrary to the prevailing tendency among experimenters to base a sweeping conclusion upon very few facts—has rendered me too exacting, but I must confess that so far I have not been able to recognize *true* internal secretions in more than three sets of organs, the thyroid, including its glandules, the parathyroids, the adrenals, and the pancreas. In these organs alone has the secretion been identified at the seat of its formation, traced to the blood-stream, and, through the blood, to all tissues. This might be said to apply to the liver, owing to its glycogenic function and to the broadcast distribution of glycogen; but in accord with Claude Bernard's original view, physiologists very properly consider the formation of glycogen as "a temporary reserve supply of carbohydrate material that is laid up in the liver during digestion and is gradually made use of in the intervals between meals."[20] Glycogen, therefore, is not a true internal secretion.

Many other organs have been regarded as sources of internal secretions. A close analysis of the question, however, suggests that while the evidence in favor of this view is very meager, many facts tend to disprove it. Investigators who have contended that these and other structures are ductless glands have, almost without exception, based their contention on the plea that extracts of these structures produce physiological effects. This accounts for the fact that practically every tissue, including muscles, nerves, lymphatic glands, and even ciliary body, nasal mucous membrane, the placenta, has been thought to produce an internal secretion. The weakness of such a plea is self-evident. Almost any organic substance will in some way or other affect the blood-pressure, and when we consider that all tissues contain more or less nuclein, intermediate, and therefore toxic, waste products, red and white corpuscles, and many other substances capable each in its own way of evoking some sort of reaction when injected into animals, the actual value of such experiments is reduced to *nil*. It is about as scientific as the giving of hashed ear for earache.

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[20] Howell: "Textbook of Physiology," p. 725, 1905.

Finally, and quite in keeping with the above remarks, is that those of the organic products which are to any degree toxic may, through the adrenal system, evoke an auto-protective reaction the symptoms of which seem to the investigator the expression of a physiological function which he credits to the extract used, supposedly an "internal secretion." On the other hand, beneficial effects are sometimes obtained through the fact that certain tissues combine the properties of two or more internal secretions, the posterior pituitary lobe, for instance, which is rich not only in chromaffin or adrenal substance, as stated, but also in nucleins, owing to its wealth in nervous elements.

Some of these physiological effects will be brought out under the remaining headings of this chapter.

THYROID ORGANOTHERAPY.

When, in the light of the data submitted in the third chapter, we administered thyroid gland, which combines the actions of the thyroid and parathyroids, the following effects are produced: It renders the phosphorus of all tissues, and all free substances, such as bacteria, wastes, toxins, etc., containing phosphorus, more inflammable or sensitive to the action of the oxygen in the blood. As this applies particularly to nerves and nerve-centers (all of which are especially rich in phosphorus) the adrenal center and therefore the adrenals themselves are excited, and, the adrenal secretion being the agent which takes up the oxygen of the air to sustain the blood's oxygenizing power, the supply of oxygen is also increased. All the various phosphorus-laden substances are thus not only rendered more readily oxidizable by thyroid extract, but this remedy also provides indirectly the required oxygen. This is not all, however. As the functions of all organs are enhanced by this process, the pancreas and the leucocytogenic organs are also stimulated, and trypsin and phagocytes, which are the active destroyers of pathogenic organisms, toxins, and other poisons, are also increased. Briefly, under the influence of thyroid preparations, we have in the blood—and demonstrable therein—all the active agents concerned with *metabolism, nutrition,* and *immunity:* an increase (1) of adrenal oxidizing substance, or adrenoxidase (the albuminous constituent of hæmoglobin; Ehrlich's amboceptor); (2) of thyroid sensitizing substance (Wright's opsonin); (3) of trypsin (Ehrlich's complement and Metchnikoff's cytase) and (4) bacteriolytic leucocytes (Metchnikoff's phagocytes).

When, therefore, thyroid preparations are given in small doses, we may expect the following phenomena, especially when the remedy is given in cases of hypothyroidia:—

A *rise of temperature* due to the increased oxidation brought about by the thyroid and adrenal oxidizing substances acting jointly; *enhanced metabolism* a normal result of the augmentation of general oxidation, with *increased appetite* due to the resulting greater demand for foodstuffs. A marked improvement in *general nutrition* and *strength* is a self-evident result of the assimilation of a greater proportion of food-materials, and the *rapid growth* likewise where, as in cretinism, it is stunted. The *cerebro-spinal system* is particularly influenced owing to its wealth in phosphorus; there is, in suitable cases, *development of intelligence.* All organs being the seat of increased metabolic activity and nutrition, the intestinal, renal, cardiac, and cutaneous and hepatic functions are all enhanced. Even the hair grows bountifully not only in cretinism, but when its loss is due to impaired nutrition of thyroid origin. It counteracts *premature senility* in all its phases by restoring to the organism the main constituent which sustains, with the co-operation of the adrenoxidase, the functional efficiency of all its parts.

In large doses, on the other hand, thyroid preparations produce quite the opposite effects. By imposing hyperoxidation upon all cells, these are catabolized or broken down before they can be adequately built up, *i.e.*, anabolized, and, instead of increased nutrition, we behold gradual emaciation beginning with the adipose tissues. Hence the use of thyroid gland in obesity.

Small doses are, therefore, indicated in all cases to begin with, 1/12 grain (0.005 Gm.) sufficing in mild cases, and in marked ones, 1 grain (0.066 Gm.) of the desiccated thyroid (U. S. P.) in adults, for example, and 1/2 grain (0.033 Gm.) in children over 2 years old. Gradually, the dose may then be increased, remembering that 3 grains (0.2 Gm.) three times daily should not be exceeded. Each grain of the desiccated gland contains 5 grains (0.33 Gm.) of the gland in its fresh state. Kendall's thyroxin,[1] is not as yet available on the market.

When thyroid preparations are judiciously used, that is to say, when their action is controlled by giving only carefully adjusted doses, aided by the concomitant use, if needed, of other agents—iron, for example—to supply the hæmatin necessary to build up the hæmoglobin molecule; when also with thyroid we wish to increase the albuminous moiety of that molecule, strychnine when the blood-pressure is too low to insure adequate tissue nutrition, etc., results are obtained which soon convince the clinician that they constitute a very valuable addition to our armamentarium. Especially does this obtain:—

1. In diseases due to slowed destruction of toxic wastes, as shown by its action in tetany, epilepsy, eclampsia, disorders of menopause, asthma, chronic rheumatism, migraine, and also by those due to slow oxidation of fats, as in obesity.

2. In diseases due to lowered general nutrition of all tissues, including the bones, as shown by its action in hypothyroidia, cretinism, myxœdema, and kindred disorders in which calcium metabolism obtains—osteomalacia, rickets, and osteomyelitis.

3. In disorders due to lowered nutrition of the muscular elements, including the skeletal and vascular muscles, as shown by its action in general adynamia, neurasthenia, and myasthenia.

4. In all cases in which the processes of repair or absorption are deficient, as shown by its action in delayed union of frac-

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[1] Kendall: Endocrinology, April, 1917, and April-June, 1918.

ures, certain benign and malignant neoplasms, and syphilitic tissue and bone necrosis.

5. In infectious diseases—owing to the increase of auto-antitoxin, thyroiodase (opsonin), and phagocytes—as shown by its action in the early stages of tuberculosis, typhoid fever, infectious tonsillitis, and certain exanthemata.

The majority of the disorders enumerated above, apart from those already reviewed, will be found treated at length in the second volume. In the following pages, however, I will include only those conditions which in addition to those studied in the third, fourth, and fifth chapters of the present volume, and in the second volume, are of special practical importance as a field for thyroid organotherapy.

INSANITY.—What data we possess on the relations between mental disorders and the thyroid apparatus indicate that both hypothyroidia and hyperthyroidia are equally fruitful in the genesis of many psychoses. Could we clearly establish a line of demarkation between these two states, however, their study would present no difficulty; but such is not the case in the light of prevailing views. Thus the classic symptoms of myxœdema may be accompanied, especially in the advanced stage, by mental disorders which are not in keeping with the asthenic phenomena that belong to hypothyroidia. The report of the Committee of the Clinical Society of London showed, for instance, that, while a certain proportion of cases of myxœdema suffered from melancholia, the one mental disorder we should expect to find in such a depressive state of the thyroid apparatus, the majority suffered from dementia, acute and chronic mania, delusions, and hallucinations, all of which denote some degree of functional erethism.

Nor do we obtain aid through the morbid histology of the thyroid in insane cases. As stated by Ramadier and Marchand,[1a] after an examination of 278 thyroid glands of patients who had died in four different asylums, it is impossible to establish any constant relation between the thyroid changes and the form of mental disease from which the patient suffered.

Yet, there is much to be discerned and there are many therapeutic hints to be garnered when these cases are interpreted from the standpoint of the views defended in the present work. Thus, taking the influence of the thyroparathyroid mechanism upon oxidation and metabolism as factors of the problem, we have in hypothyroidia such mental states as melancholia, hypochondria, and apathetic delusional insanity, with perhaps ideas of suspicion. What mental disorders are witnessed in the more advanced stage of myxœdema are also commonly characterized as melancholia. So marked is the depressive state in these cases, in fact, that the late Lloyd Andreizen[9] was led to assert that various insanities having a constant and distinct physiognomy grew in the soil of acromegaly and myxœdema. "In the one case (myxœdema)," he wrote, "a morbid process starting from the thyroid gland affected the whole capacity of the blood in regard to its power of taking up oxygen from the air. On examining the blood with the mercurial pump, it was found that its oxygen and carbonic acid were much diminished, and, by placing the individual in the apparatus for examining the gases of respiration, it was found out that he took in but little oxygen and correspondingly gave out but little carbonic acid during life." That this sustains my own view that the thyroid, partly through its influence on the adrenals, influences tissue respiration is obvious. But this, in itself, sustains Andreizen in his conclusion that certain mental disorders grow in the soil of myxœdema. In other words, we should look upon hypothyroidia as one of the causes of depressive mental states.

[1a] Ramadier and Marchand: L'Encéphale, Aug., 1908.

This, however, fails to account for the opposite phenomena, *i.e.*, those we associate with erethism, mania, dementia, and the various manifestations in which irritability and excitement are prominent. But these signs are also explained by my conception of the functions of the thyroparathyroid apparatus, *i.e.*, that it acts as opsonin to insure the destruction of toxic wastes. Oxidation and metabolism, particularly its catabolic phase, we have seen, being impaired by the existing hypothyroidia, we have an accumulation of toxic wastes in the blood, and it is to the morbid influence of these poisons on the brain that all manifestations, in myxœdema, such as mental excitement, persistent hallucinations or delusions, and mania, must be attributed. Here, again, Andreizen struck the keynote of the problem, in my opinion, when, in his study of the relations of autotoxin in its bearing upon insanity, to which the previous quotation belongs, he referred to the presence with weakness, dullness, and subnormal temperature "of a tendency to the accumulation of incompletely oxidized bodies (fat, etc.)" in the tissues. Correct also, from my viewpoint, were the estimates of Bruce,[3] who, in reporting the results of thyroid treatment in 60 cases, attributed the improvement noted to the production, by the remedy, of a febrile state—quite in keeping with my own view (see page 628) that the thyroid and the adrenals are active in the genesis of fever.

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[9] Andreizen: Quoted by Hamilton: Medical Record, April 29, 1899.

Such being the case, we can conceive how myxœdema and hypothyroidia can become the soil not only for depressive mental disorders, but also for those in which excitement and cellular erethism prevail. It follows also that hypothyroidia should be considered as a prominent factor in the genesis of insanity. Having in myxœdema undeniable proof of the influence of the thyroid apparatus on the mental equilibrium and a rational explanation of the pathogenic process, the physiology of these, particularly the important rôle in immunity, should no longer be neglected by psychiatrists. Laignel-Lavastine[4] closed an able study of this subject by the statement that "the existence of glandular disorders in psychical syndromes has not as yet, in my opinion, attracted sufficient attention. Nevertheless the existence of such disorders in certain cases is undeniable." Frankl Hochwart[4a] also lays stress upon this connection.

Recently, L. Vernon Briggs[5] wrote more pointedly, emphasizing both the rôle of autointoxication and the neglect of this important factor in mental disease: "In many large public and private institutions those in charge receive early cases of mental disturbance, and watch the toxæmia verge into mania, catatonia, and dementia; they notice the acetone breath and are aware of the true condition; but little if anything is done to stay the progress of the disease, and to save these individuals."

As to treatment of this class of psychoses, there is good ground for the belief that, intelligently employed in suitable cases, considerable help can be gained from thyroid preparations.

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[3] Bruce: Journal of Mental Science, Oct., 1895.

[4] Laignel-Lavastine: La Presse médicale, Aug. 1, 1908.

[4a] Frankl Hochwart: Amer. Jour. of the Medical Sciences, Aug., 1912.

[5] L. Vernon Briggs: Lancet-Clinic, Jan. 28, 1911.

McLane Hamilton,[6] who, with Andreizen, attributes various forms of insanity associated with disease of the thyroid gland to autointoxication, refers to his own experience and to that of Babcock,[7] Clark, and others to the therapeutic value of these agents. In cases of stuporous melancholia, cerebral exhaustion, and chronic disturbed states of an asthenic type, there was a prompt lighting up of the mental condition, elevation of the temperature, and an increase of hæmoglobin in some instances of over 20 per cent. They were also found useful in chronic insanity with erotic delusions and psychoses in which the complete symptom-complex of catatonia was present, and also in cases of climacteric despondency. Easterbrook,[8] using thyroid in 100 cases which had proved intractable by other methods, obtained 12 per cent. recoveries. He found it more effective in women than in men, the best results being obtained in mental disorders connected with childbearing. Of 22 patients treated by Leeper,[9] 12 recovered; only 1 of these required readmission subsequently, all others being, as far as he could ascertain, permanently relieved. Conversely, A. W. Wilcox[10] did not obtain satisfactory results. His beginning daily dose was 15 grains (1 Gm.), increased daily by 15 grains (1 Gm.) until 60 grains (4 Gm.) were given daily.

Very valuable in this connection is a report by Mabon and Babcock,[11] based on the results of thyroid treatment in 1032 collected cases of insanity, in which the following conclusions are reached: 1. The dose of the extract depends entirely on the individual case. In some cases 25 grains (1.65 Gm.) three times a day will be necessary to bring about a circulatory or temperature reaction, while in others the same results may be had with the use of 5 grains (0.33 Gm.) *t. i. d.* Each case must be a law unto itself. 2. It is essential that the patient should be placed in bed to obtain the best results, and he should be continued there during the entire treatment and for a week following its discontinuance. 3. The treatment should be continued for at least thirty days. 4. We should not be discouraged by failure in the first administration, but should resort to two, three, or more trials, if necessary. 5. The most gratifying results in thyroid treatment are to be obtained in cases of acute mania and melancholia with prolonged attacks, puerperal and climacteric insanities, stuporous states and primary dementia, particularly where these forms of mental alienation do not respond to the usual methods of treatment. 6. A high temperature reaction is not essential, as the average maximum temperature in the recovered cases among men was 99.6°. 7. Physical improvement is the outcome in most cases whether mental improvement takes place or not. 8. The proportion of individuals who recover under thyroid treatment and then relapse is less than the proportion that relapse after recovery from other methods of treatment. In a series of his cases only one patient who had recovered has relapsed.

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[6] McLane Hamilton: Medical Record, April 29, 1899.
[7] Babcock: New York State Hospital's Bulletin, Jan., 1896.
[8] Easterbrook: Scottish Med. and Surg. Jour., Dec., 1900.
[9] Leeper: Medical Press and Circular, July 5, 1905.
[10] Wilcox: London Lancet, May 20, 1899.
[11] Mabon and Babcock: American Journal of Insanity, Oct., 1899,

I would urge in this connection that *small* doses of desiccated thyroid, 1 grain (0.066 Gm.), increased only if necessary to 2 grains (0.13 Gm.) at most, be used in these cases. Those who have criticised the use of thyroid in psychoses erred in this direction and brought on, by excessive doses, the very untoward phenomena which they deplore, by loading the blood with pathogenic wastes.

Hypodermoclysis or enteroclysis should also be used periodically to facilitate osmosis and hasten the elimination of all wastes through kidneys, intestines, and skin.

Again, it should be remembered that—at least according to my views—the use of thyroid gland enhances the vulnerability of the organic phosphorus to oxidation, and that, therefore, the consumption of this element is greatly augmented by this agent, as is well shown by the increased elimination of P_2O_5. This loss should be compensated for, particularly in depressive mental states (the brain-cells being rich in phosphorus), by administering lecithin, or glycerophosphate. Berkeley,[12] though unaware of my explanation of the influence of thyroid on tissue phosphorus, found lecithin very valuable in catatonia when given in conjunction with small doses of desiccated thyroid.

In dementia præcox we have the opposite condition, *i.e.*, hyperthyroidia as an underlying cause. As Berkeley states:

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[12] Berkeley: *Ibid.*, Jan., 1909.

"Exophthalmic goiter cases and cases of catatonic dementia præcox have usually an enlargement of the thyroid gland, the bruit over the neck, the high tension and rather rapid pulse, accentuation of the second aortic sound, wide pupils, increase of the superficial and deep reflexes, and, lastly, a moderately small cell lymphocytosis."[18] The inference is obvious: excess of thyroid activity must be the underlying cause of dementia præcox. Thyroid and other organic agents proved harmful, but partial removal of the thyroid proved curative, as first shown by Berkley. The cause, whether tonsillar, dental, intestinal, etc., of the thyroid erethism, must be removed. Bayard Holmes and also myself,[18a] have cured severe cases by flushing the colon through an abdominal opening. Yet, some cases, especially those of the hebephrenic type, have been benefited by thyroid treatment, as observed by Levison,[18b] Davidson, [18c] and others.

EPILEPSY.—Certain features of the pathogenesis of epilepsy are neglected. Besides the usual array of symptoms, diagnostic points, etc., the well-worn and recognized etiological factors; intestinal worms, indigestible foods, cicatrices, dentition, fright, masturbation, alcohol, lead poisoning, syphilis, uræmia, and that great basket of iniquities, heredity, are doing duty as of old, with tumors, sclerosis, and nuclear degeneration as local lesions. The physician is enjoined to remove the cause in all conditions in which this is at all possible, to look to depressants as mainstays—with the bromides and chloral in the lead—and to think well of asylums and retreats.

The features which seem to be overlooked are peculiar in the sense that, from the standpoint of practice, they exceed all others in importance. In fact, they constitute the *deus ex machina* of the fit, as it were. Literature shows plainly, for instance, that the dominant note in the pathogenesis of the convulsions is impairment of metabolism, and that the spasmogenic agent is some toxic agent in the blood-stream. Pathological variations of vasomotor action, due more or less to a morbid condition of the blood, have also asserted themselves so strikingly in the production of fits that some observers have been inclined to regard them as the foundation of the whole symptom-complex. Again, destruction of the spasmogenic agent has been urged by some as the only reasonable principle of cure in opposition to the use of bromides and chloral, which tend to increase its formation in the blood-stream. Finally, bacterial toxins may be the underlying cause.

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[18] Berkley: *Loc. cit.*
[18a] Sajous: New York Med Jour., Feb. 14, 1920.
[18b] Levison: Hospitalstidende, No. 36, 1909.
[18c] Davidson: Australasian Med Gaz., April 20, 1911.

As to the presence of toxic wastes, so able an observer as L. Pierce Clark,[14] after a study of 150,000 seizures, concludes that "we must see the principle of pathogenesis in an initial toxin or autointoxication," *i.e.*, "an accumulation of waste products." The relationship between the latter and the production of epileptic seizures is further shown by the fact, emphasized by Van Gieson[15] and many others, that the attacks are more frequent when gastro-intestinal disorders, especially those due to overeating, gulping, and constipation, are present than at other times. Indeed, Herter[16] caused typical tonic and clonic convulsions and death in rabbits in forty-five minutes by injecting the defibrinated blood of an epileptic overfeeder, while blood from an ordinary patient did not produce such effects. Krainsky[17] also provoked characteristic seizures in rabbits in two or three minutes and several recurrences with blood-serum obtained by cupping from a case in status epilepticus. Ceni[18] found the blood of epileptics poisonous to man also. Thus, he ascertained experimentally that "non-epileptic subjects react under injections of hypertoxic serum, and present intoxication phenomena that are analogous to those observed in epileptics, though less intense and unaccompanied with psychic disorders or epileptic attacks."

The effect of such poisons on the *vasomotor mechanism* is quite as evident. The conjunctiva and face of the epileptic from whom Herter obtained the hypertoxic serum referred to were congested. That this was due to the action of the poison in his blood is shown by many facts. "Certain drugs, notably absinthe," writes Schäfer,[19] "produce, when injected into the vascular system, convulsive attacks which are scarcely distinguishable from the epileptic fits provoked by stimulation of the cortex cerebri." Now, all such drugs cause a marked rise of the blood-pressure. This may be shown by comparison with a few of the many other spasmogenic drugs. Thus, while absinthe was found to cause intense congestion of all organs examined by Pauly and Bonne,[20] Wood[21] states that "the full dose of strychnine produces a rise of the arterial pressure which is enormously increased during the convulsions." He refers also to the observation of Bezold and Bloebaum, "that when a small dose of atropine is injected into the carotid artery near the vasomotor centers" . . . "there is an instantaneous rise of blood-pressure"—"a great rise," he subsequently remarks. Cocaine, as shown by von Anrep, causes "convulsive movements of cerebral origin" which "are arrested by section of the spinal cord." Wood also says: "Certainly the evidence is overwhelming that cocaine directly increases the blood-pressure." The fits caused by this drug are precisely those of epilepsy; the syndrome is known, in fact, as "cocaine epilepsy."

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[14] L. Pierce Clark: Medical News, July 18, 1903.
[15] Van Gieson: Cited by House: Buffalo Medical Journal, June, 1898.
[16] Herter: Jour. of Nerv. and Ment. Dis., Feb., 1899.
[17] Krainsky: Wiener klin. Woch., Feb. 24, 1898.
[18] Ceni: Rivista Sperimentale d' Freniatria, vol. xxxi, Fasc. ii, 1905.
[19] Schäfer: "T. B. of Physiol.," vol. ii, p. 721, 1900.

In typical epilepsy the participation of the vasomotor mechanism is none the less marked. Spitzka, over thirty years ago (1881), attributed the epileptic seizures to the "explosive activity of an unduly irritable vasomotor center," and most neurologists regard epilepsy as "a functional vasomotor disease." The blood-pressure is not only high, as observed by François-Franck and Pitres, but the speed of the blood-stream in muscular vessels, according to Leonard Hill,[22] is from three to five times greater than usual—an index of the violence of the cortical circulation. Indeed, Weber[23] found vascular lesions and extravasations in the cortex and medulla of cases of status epilepticus, so great was the force which urged the blood into the capillaries. Onuf even found, besides the capillary changes, tortuosity and aneurismal dilatations. Victor Horsley[24] has emphasized the importance of congestion of the cortical mantle in the production of epileptic seizures. Ito[25] caused them in guinea-pigs by producing traumatic hyperæmia of the cortex.

We thus have, as cause of the convulsions, a toxic in the blood capable of producing a high vascular tension, and thereby excessive hyperæmia of the cortex. This hyperæmia is a recognised cause of epileptic seizures; in fact, as shown by Prus,[26] even electrical excitation of the cortex cannot provoke fits after it has been anæsthetized by a local application of cocaine. This is not intended to mean that a high vascular tension due to toxics of internal or external origin will produce epileptic seizures in every one and any one; were it so, the many disorders of the gout series would likewise provoke them. What I do mean is, that in all epileptics *the exciting factor of the seizures themselves,* and irrespective of the condition which renders the subject liable to them, *is a poison formed in the tissues or food residues, toxalbumins,* and that our chief aim, if we are ever to obtain mastery of the dread disease, should be to destroy these poisons and prevent their formation. Is it by saturating the system with bromides—which lower oxidation—that this can be accomplished? Such treatment ignores nature's danger-signals, and gives the spasmogenic poison free sway.

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[20] Pauly and Bonne: Gaz. hebd. de méd. et de Chir., May 13, 1897.
[21] Wood: "Therapeutics, Its Principles and Practice," 12th ed., p. 217, 1905.
[22] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 155, 1900.
[23] Weber: Wiener med. Woch., Bd. xlix, S. 153, 1899.
[24] Victor Horsley: British Medical Journal, April 2, 1892.
[25] Ito: Deut. Zeit. f. Chir., Aug., 1899.

What are the weapons at our disposal that are capable of causing the destruction of these poisons and of preventing their formation?

Textbooks on the practice of medicine, including the "last editions," continue, regardless of the admonitions of men of large experience to the contrary, to advocate the use of bromides as a *curative* measure. Percy Bryant,[27] ten years ago, emphasized the fact that the bromides had added another disease in many epileptics, namely, bromism. Spratling,[28] as the result of a close study of several thousand cases at the Craig Colony, concluded that "we must not only regard the bromides as powerless to cure epilepsy," but also "as capable of doing as much harm as they do good as they are ordinarily administered." F. Peterson[29] has reported 11 cases in which the number of attacks was greatly reduced by withdrawal or marked reduction of the drug: "in some cases," says this neurologist, "the improvement is startling."

In the light of the evidence I have submitted in the foregoing pages, the untoward effects of the bromides are readily accounted for. The seizures are due to the presence in the blood of toxic waste products which, by powerfully exciting the vasomotor center, cause an intense rise of vascular tension and violent hyperæmia of the cortex. The logical indication is to prevent the formation of these toxic wastes by measures that enhance the oxidation processes through which they are converted into harmless, readily eliminated end-products. Now, the bromides produce precisely the opposite effect: Wood[30] states that "even small doses of bromide are directly depressant to the circulation." Again: "In mammals the bromide acts very much as on frogs, inducing progressive paralysis, depression of temperature, and death by asphyxia when given in small poisonous doses." Asphyxia here clearly points to the drug as one that impairs oxidation, a fact emphasized by the lowered temperature. Chloral, also used considerably in epilepsy, is fully as harmful; Richardson, Hammerstein, and others have found that it could reduce the temperature very greatly—6° C. (10.8° F.), according to the last-named observer.

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[26] Prus: Wiener klin. Woch., Sept. 22, 1898.
[27] Percy Bryant: State Hospital Bulletin, Oct., 1896.
[28] Spratling: New York Medical Journal, Aug. 19, 1905.
[29] F. Peterson: *Ibid.*, Sept. 25, 1897; and Amer. Med., June 24, 1905.

Of major importance in this connection is the fact that the bromides paralyze a mechanism which, from my viewpoint, is the patient's sheet-anchor, viz., the adrenal system. This action is sufficiently marked in some instances to cause bronzing similar to that observed in Addison's disease. Bourneville and Chapotin,[31] for instance, refer to Echeverria,[32] who witnessed a case in which the brow and neck "were markedly pigmented brown," and to others reported by Voisin; in one of these "the skin of the face was a dark, dirty yellow"; in another it was "covered with bronze patches having no connection with the acne." Inasmuch as it is the adrenal secretion which takes up the oxygen of the air to carry on oxidation (as the albuminous constituent of hæmoglobin) throughout the entire organism, the bromides—chloral as well—inhibit precisely the function which should be activated.

On the whole, it is by preventing the destruction of the toxic wastes which provoke the fits that these drugs are harmful, and it is obvious that their use, under the delusion that they are curative, can only serve to perpetuate the disease unless used, as shown below, with the greatest discretion.

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[30] Wood: "Therapeutics," 13th ed., p. 244, 1906.
[31] Bourneville and Chapotin: Le progrès méd., Jan. 6, 1900.
[32] Echeverria: Philadelphia Medical Times, Nov. 23, 30; Dec. 7, 14, 1872.

Another very important feature in the treatment of these cases, however, is the diet. In some of my cases this alone sufficed to reduce the number of paroxysms from several a day to one or two a week, and in one instance to cause their cessation as long as the patient abstained from the use of certain foods and beverages, including coffee and tea. The general principle involved in this connection is that we are dealing mainly with poisons formed during the breaking-down of worn-out living substance, *i.e.*, during catabolism, and that these poisons form owing to insufficiency of those constituents of the blood which carry on catabolism and destroy the toxic wastes. In the majority of cases the food-intake is excessive, and the cellular elements are burdened with detritus which cannot be completely converted into eliminable products. The blood, therefore, is loaded with substances which irritate the vasomotor center and thus provoke the seizures.

The practical lesson of this principle is obvious, namely, to allow the patient only the quantity of food strictly necessary to the needs of the body. Indeed, neurologists of wide experience have found that the best results are obtained when the food consists mainly of cereals, milk, fruits, and butter. Some include eggs, but others object to them. Meat, if allowed at all, should be strictly limited to the midday meal, and even then in small quantities. Fats, fried foods, and pastry often prove harmful. Stimulants which tend primarily to cause a rise of the blood-pressure, *i.e.*, alcohol, coffee, and tea, should not be allowed. Gastro-intestinal disorders sometimes suffice to awaken the disease. Appropriate treatment, including daily colon-flushing with normal saline solution, has proven curative in such cases. The patient should also be enjoined to drink water freely, in order to facilitate the elimination of wastes.

As to the medicinal treatment, the indications are remedies which, as I have pointed out elsewhere,[34] enhance oxidation, the beneficial effects of thyroid extract in tetany, tetanus, and puerperal eclampsia affording ample proof of their value. Bourneville[35] found that thyroid extract failed to arrest the seizures, and even increased them. But the cause of this is self-evident: he gave full doses, and thus enhanced general metabolism so actively that he increased the production of wastes. Browning,[36] on the other hand, caused the cessation of convulsions in epileptics by giving ¾-grain (0.05 Gm.) doses twice daily. He states that these cases "are due to or associated with disturbances in the general metabolism of the body" and refers to them as "pseudo-epilepsy." All cases of idiopathic epilepsy should be considered in the same light if the term "pseudo-epilepsy" were warranted at all, since, as we have seen, Pierce Clark and others ascribe the disease to "an accumulation of waste-products." Browning's cases were *bona fide* cases of epilepsy, and what they do teach is that small doses of thyroid extract are alone indicated. These, however, as my own observations have shown, must be *very gradually* increased according to the effect on the patient. I usually begin with 1 grain (0.066 Gm.) at each meal, giving a small dose of sodium bromide on retiring at first, if necessary, and gradually reducing the dose until none is given at all. Some cases are benefited by larger doses of thyroid. Thus, in a case treated by a colleague, under my supervision, the nurse, through a misinterpretation of instructions, doubled the dose; the result was considerable improvement. Söchting[36a] obtained remarkable results also in a case in which hypothyroidia was evident—the underlying cause of cases cured with thyroid.

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[34] Sajous: "Internal Secretions and the Principles of Medicine," p. 769, 1903; Monthly Cyclo. of Pract. Med., Jan., 1903; Jour. Amer. Med. Assoc., Feb. 4, 1905.

Osborne[37] also refers to a number of cases of epilepsy treated successfully with thyroid, several cases being in women at the time of the menopause and in young girls at the time of puberty. There being no assignable lesions for the epileptic attacks, "I reasoned," says this clinician, "that they must be purely toxic, and that this toxæmia was in excess periodically when the patient should have menstruated. Many of these patients had received bromides, and, while this postponed or controlled the epileptic attacks, general debility and bromism were appearing. In the young girls I used thyroid as an emmenagogue, with the belief that normal menstruation would prevent the attack of epilepsy. I found that it did. I then used the thyroid in the menopause cases, in some continuously in small doses, and in others a few days a month at a possible menstrual epoch. I found that I could control and prevent the epileptic attacks as well with thyroid as could be done with bromides, and with much better results to the system." Similar cases have been reported by A. Gordon;[37a] Sicard[37b] found that bromides counteracted actively the effects of thyroid, while Manson[37c] noted the marked value of thyroid in the epilepsy of cretins—a suggestive relationship.

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[35] Bourneville: Le progrès méd., vol. xxiv, p. 20, 1896.
[36] Browning: Jour. of Nerv. and Ment. Dis., Oct., 1908.
[36a] Söchting: Medizin. Klinik, May 1, 1910.
[37] Osborne: Jour. Amer. Med. Assoc., Nov. 3, 1906.

Briefly, the treatment of epilepsy should have as main object, as I pointed out in 1903,[38] *to activate the catabolism of spasmogenic wastes through the adrenal system* and to avoid, *as a cure,* drugs such as the bromides and chloral, which depress this function. In some instances, the iodides serve a better purpose; the salicylates (or salicin, 5 grains [0.33 Gm.] three times daily) are also effective, as Haig, Vincent,[39] and others have shown, but both these agents stimulate the adrenal center and enhance, therefore, the oxidation processes. Such remedies, to keep the blood free of toxic wastes; dietetic measures, to reduce the quantity of such wastes formed; and finally, the free use of water, to insure the rapid elimination with the urine, sweat, etc., of all physiological wastes, constitute a therapeutic triad which soon causes the vasomotor center to lose its irritability, thus preventing the cortical hyperæmia to which the convulsions are due. A small dose of strontium bromide at night, to reduce the hypersensitiveness of the vasomotor center, may be used, but if progress is made without it no bromide had better be given.

Isolated cases in which thyroid proved of value have been reported by a number of observers, who in most instances specify that the bromides had proven ineffectual. A series of 6 cases in which hypothyroidia was discernible were treated by A. Gordon.[40] In these cases a remarkable change took place, both in the general condition and in the frequency of the epileptic seizures. On the other hand, Pierce Clark[41] used thyroid in 5 cases, which failed to be "attended with very good results." Two points stand out prominently in these cases: (1) the dose was too large, the initial dose being 5 grains (0.33 Gm.) *t. i. d.*, and (2) cases were selected "in which epilepsy had been a prominent feature in the patient's life since early infancy." Obviously, in the latter instances we were dealing with advanced gliosis, which precluded all hope of cure. Yet, as Pierce Clark says, "all seemed to be benefited for the time being." Dercum[41a] found as small doses as 1/8 to 1/4 grain (0.008 to 0.016 Gm.) for prolonged periods very helpful.

[37a] Gordon: Penna. Med. Jour., Feb., 1910.
[37b] Sicard: Jour. de méd. de Paris, Nov. 19, 1910.
[37c] Manson: Med. Record, Jan. 1, 1910.
[38] Sajous: *Ibid.*, p. 769, 1903; Monthly Cyclo., Jan., 1903; Jour. Amer. Med. Assoc., Feb. 4, 1905.
[39] Vincent: Journal of Mental Science, April, 1904.
[40] Gordon: Therapeutic Gazette, Dec., 1907.
[41] Clark: Medical Record, Oct. 24, 1896.

In some cases the causative toxæmia is primarily due to toxins derived from intestinal stasis, carious teeth, chronic sinusitis or tonsillitis and other processes of bacterial origin. Search should be made for any pathogenic factor and if any be present, it should be eradicated. In cases of cecal or colonic stasis ascertained by X-ray barium meal examination, high colonic flushing is very helpful, in addition to the thyroid treatment and may be curative, as observed in a personal case.

OBESITY.—The fact that thyroid preparations in sufficient doses promote the rapid combustion of fats has caused them to be used extensively in this disorder. Given indiscriminately and empirically, in excessive doses, their use has often been attended by distressing after-effects.

The cases in which thyroid gland is scientifically indicated are those in which some degree of hypothyroidia exists, and in women in whom panhysterectomy, by removing two organs rich in adrenal rests, the ovaries, has greatly reduced the oxidative power of the blood—a deficiency which affects morbidly the thyroid apparatus as it does all other tissues. In the latter class of cases, therefore, hypothyroidia is also the foundation of the obesity. This may be said also of destructive disorders of the pituitary body which, by depriving the thyroid of its functional impulses, reduce its functional activity. Briefly, in all cases of obesity in which thyroid gland is rationally indicated, the feature to determine is whether directly or indirectly hypothyroidia underlies the adiposis.

In very mild cases, the underlying cause is sometimes difficult to determine; but as a rule, some, very few perhaps, of the typical signs of hypothyroidia may usually be discerned on close

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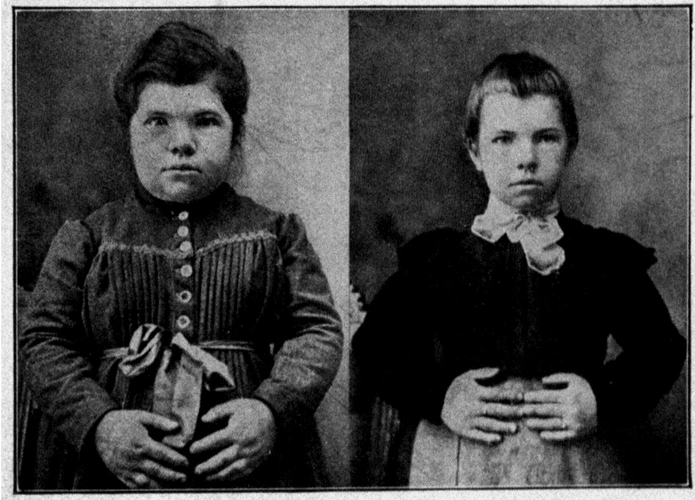
[41a] Dercum: Jour. Amer. Med. Assoc., lxvii, p. 257, 1916.



CRETINIC OBESITY.

Case of cretinism aged 21. Effects of four months' thyroid treatment. [Sanderson.]

inquiry. These are chilliness and subnormal temperature, coldness of the extremities and sensitiveness to cold; fatigue on slight exertion; constipation with tendency to tenesmus; more or less frequent attacks of migraine, "sick headaches" with nausea, vomiting, etc., and other periodic manifestations of auto-intoxication—due to inadequate reduction of waste-products and their retention in the blood. The skin taking part in the process of elimination, urticaria and eczema may be found in the history of the case, while transitory œdemas of the brow, around the eyes, and sometimes of the face, even in the absence of albuminuria or casts, may also have occurred. Enuresis is commonly observed in fat, pasty children of this type and may persist to adult age. The patient may be subject to frequent catarrhal disorders of the respiratory passages, usually ascribed to colds, but due mainly to vascular and glandular relaxation. A tendency to early alopecia, including the eyebrows (especially their outer third), is also noticeable in some instances—a sign of deficient general nutrition which coincides with a marked proclivity to early senility. The supraclavicular pads are sometimes discernible when the adiposis is not excessive. Even in the latter case sometimes the pads project beyond the general level.

In women, the menstruation appears late owing to retarded development, and there is a proclivity to metrorrhagia due to laxity of the muscular coats of the uterine arterioles, while pelvic disorders are apt to occur owing to deficient support of the uterus, lack of tone in its muscular elements. Leucorrhœa is also frequent owing to relaxation of the glandular elements of the whole genital tract. Such women conceive readily, but abortion is very frequent among them; if the fœtus is carried to the normal period, they have little or no milk. If the obesity is marked, sterility is the rule; but when such patients are given thyroid gland and their obesity is reduced, they readily become pregnant, as observed by Hertoghe, Montgomery, and others.

Cases of obesity due to hypothyroidia also afford, as a rule, quite a clue as to the presence of this condition, by the statement that none of the dietetic "cures" seemed to improve their condition. Indeed, most of them complain of having been made worse. This is readily explained by the fact that their hypothyroidia could only be aggravated by deficiency of food and forced exercise.

Contraindications to the use of thyroid preparations in obesity have been elaborated by various observers; but perusal of their work indicates clearly that they have been administering excessive doses. Several lives have been lost under these conditions, and many others have been lost by self-drugging. Large doses are always dangerous in the obese, since the heart is itself invariably fatty, while, conversely, small doses are always helpful because they very gradually rid the heart of the fat which compromises its functions and eventually causes death—when the patient has not been carried off by some intercurrent disorders. Even moderate doses have not proven harmful when the patient was under medical surveillance.

The *dose* of desiccated thyroid need not exceed 1 grain (0.066 Gm.) three times daily in any case. This suffices to cause a decrease of weight of from 1 to 3 pounds a week, and sometimes more, Anders[43] having observed in 2 cases under this dose "a progressive loss of weight at the rate of 4 to 6 pounds per week, respectively, without injury to the general health." Such doses do not impose upon the patient the need of modifying his usual mode of living and his diet need not, unless excessive, be altered. Occasionally, the dose must be gradually increased to 2 grains (0.13 Gm.) three times daily, but this is seldom necessary.

When the obesity is accompanied by weakness, the appetite is usually increased, especially when, as is my custom, $^{1}/_{50}$ grain (0.0013 Gm.) of strychnine is given with each dose of desiccated thyroid. The patient does best under these conditions, when lean meats, plainly broiled, roasted, or stewed, constitute the increase of his dietary. This treatment is valuable in another direction: it tends to counteract any tendency to constipation that may be present.

The *untoward effects* most frequently met with in obese subjects are of cardiac origin: marked discomfort in the precordia; dyspnœa, with tendency to heart-failure. In some instances this has been followed by death, when marked fatty degeneration happened to be present. But, as stated, these do not occur when small doses—1 grain (0.066 Gm.) of the desiccated thyroid—are used. Even the greatest watchfulness will not prevent toxic effects when large doses are administered, since the accumulation of the thyroid principle proceeds at a rapid rate and the milder symptoms of thyroidism are almost at once followed by its acute manifestations—those previously described.

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[43] Anders: "Practice," 8th ed., p. 1276.

Adiposis Dolorosa; Dercum's Disease.—Having had no personal experience in the treatment of this rare disease, the following quotation from a comprehensive article by Professor Dercum, soon to appear, is presented:—

"In the treatment of adiposis dolorosa one remedy has in a few cases proved of value, and that is thyroid substance. This should be given in doses of from 2½ to 5 grains (0.165 to 0.33 Gm.) three times daily, for a very long time. The salicylates, notably aspirin, are of decided value in relieving the pain. The best plan of procedure, as a matter of course, is to place the patient in bed, and to institute a systematic course of treatment. The rest should be absolute and should extend over several months of time.

"The patient should be weighed when treatment is begun and thyroid substance given at first in small and then in somewhat larger doses. At the same time a diet should be instituted that is largely free from carbohydrates and fats. It should be remembered, however, that a diet, no matter how rigid, will of itself make no impression in adiposis dolorosa; it will fail absolutely. It is, of course, wise to institute a careful diet, but patients do better when the diet is not too strict. Inasmuch as the affection is attended by a marked asthenia, the diet should be nutritious. It should consist of the red meats in moderation, the white meats freely, the succulent vegetables, eggs, and skimmed milk. The latter can be used between meals, and, if necessary, also at mealtimes.

"The pains are not infrequently controlled or, at least, made better by aspirin or salophen in full doses, 10 or 15 grains (0.66 or 1.0 Gm.) three times daily after meals. Sometimes the tenderness and soreness are better borne when the limb or part affected is gently supported by a flannel roller; if the tenderness be extreme a layer of cotton-wool may first be applied.

"Just as soon as the tenderness permits, gentle massage should be instituted; sometimes this can never be employed; in other cases, again, it can be instituted comparatively early, and there can be no doubt that in a measure it favors the diminution of the swellings, especially if the patient can bear deep kneading. Bathing between blankets, as in ordinary rest treatment, should also be carried out, but of themselves baths accomplish nothing in adiposis dolorosa; indeed, the physical exertion and manipulation attendant upon the application of ordinary hydrotherapeutic measures in these cases exhausts the patient.

"It is a good plan to keep a record of the pulse and temperature during thyroid administration, although the writer has never observed any fluctuations of moment in these cases, even when the thyroid was pushed. The patient should, of course, be weighed from time to time, and the dose of thyroid modified according to the impression made. In some cases no impression whatever can be made; in other cases, again, the impression is decided. In 3 cases of the writer the result was most satisfactory; 2 of these were treated systematically by rest in bed; the third could not, for certain reasons, be put to bed. In all 3 the improvement in the size of the swellings and in the lessening of pain was very great. Treatment was carried out six months to a year. In 1 case the affection recurred at the end of two years, but was again controlled. In the second, improvement and practically good health has persisted for four years. The third was greatly improved, and has disappeared from observation."

GOITER.—As Rogers[43] states: "Simple goiter, or hypertrophy of the thyroid gland, is usually considered to be a disorder which is entirely distinct from Graves's disease, and to represent a totally different pathological process; but there are many reasons for doubting this conclusion and for suggesting something of the same pathological physiology, at least, in the origin of both exophthalmic goiter and simple goiter." Yet we are confronted with the fact that thyroid preparations are often useful in goiter, whereas in the active or erethic stage of exophthalmic goiter it is harmful. This is explained, from my viewpoint, however, by the fact that we are dealing in goiter with a compensative reaction very similar to that which occurs in cases of exophthalmic goiter, as previously stated. The presence of some toxic in the blood (goiters are now generally ascribed to the presence of some unknown toxic in the drinking water of the regions in which they occur endemically) creating a demand for an increase of thyroiodase as one of the antitoxic constituents of the blood, the organ is unable to furnish it. Being subjected to undue stimulation, the local expression of which is excessive vasodilation, it becomes enlarged, *i.e.*, goitrous. Briefly, in those cases in which thyroid preparations are effective, the goiter is the result of a toxæmia which the added thyroid substance helps to counteract as one of the physiological antitoxic agents.

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[43] Rogers: Annals of Surgery, Dec., 1909.

In some of these cases, however, both iodine and thyroid gland seem to produce pernicious effects. Even minute doses, as observed in one of my cases, suffice sometimes to produce distressing symptoms. It is always advisable to begin, with fractions of doses and to increase gradually until the beneficial dose. Beginning with ½ grain (0.033 Gm.) three times a day, the dose can be raised gradually to 2 grains (0.13 Gm.), but in most cases 1 grain (0.066 Gm.) suffices to compensate for the inability of the organ to supply the volume of thyroparathyroid secretion required by the organism at large.

The dietetic and other measures indicated in these cases have been reviewed in full in the article on goiter, to which the reader is referred (page 243, this volume). Surgical intervention may become necessary when pressure symptoms appear. In competent hands the post-operative mortality has been practically reduced to *nil,* and when we consider that a simple goiter may assume the more formidable type of exophthalmic goiter our duty is to afford the patient this, the surest, guarantee against it when medical treatment, including the use of thyroid, fails to turn the tide toward recovery.

CHRONIC RHEUMATISM.—In the treatment of this disease we owe much to the patient labors of Léopold-Lévi and H. de Rothschild.[44]

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[44] Léopold-Lévi and Henri de Rothschild: "Etude sur la physio-pathologie du Corps Thyroide et de l'Hypophyse," 1908; "Nouvelles études sur la physio-pathologie du Corps Thyroide et des autres Glands Endocrines," 1911.

These leave no room for doubt that thyroid gland is of great value. In a series of 39 cases ranging from the ages of 12 to 75 years, 32 were greatly improved, cure being obtained in 2 severe cases. All the concomitant symptoms, such as œdema, neuralgia, etc., were favorably influenced; it increased the appetite, caused the cardiac anginas and all neural phenomena to disappear.

Two examples of the results obtained will serve to illustrate both the treatment resorted to and the doses employed. Both were cases of chronic rheumatism with hydrarthrosis. In one of these the hydrarthrosis followed a fall from a bicycle, and was the precursor of attacks of muscular rheumatism, all the joints being gradually involved in the morbid process. Notwithstanding seasons at Aix-les-Bains, Dax, and other stations, the patient became quite impotent, having even to be fed. The usual remedies proved unavailing, though aspirin and iodine seemed, at least for a while, to be of some benefit. The patient's condition becoming steadily worse, thyroid extract was tried, beginning with 1½ grains (0.1 Gm.) every other day during ten days, followed, after five days, by resumption of the remedy; then giving again only 1½ grains (0.1 Gm.) every other day. This dose was gradually increased until, eleven months later, the patient was taking 7½ grains (0.5 Gm.), in divided doses, daily. Good results have also been recorded by Revilliod, Lancereaux, and others.

The interpretation of the pathogenesis of rheumatism I submit elsewhere in this work affords an explanation of the manner in which these results are obtained. Briefly, from my point of view, rheumatism is due to the presence in the blood of any toxin, or toxic, especially toxic wastes derived from excessive tissue metabolism, capable of exciting violently the adreno-thyroid center, and of increasing to an abnormal degree, therefore, the functional activity of the adrenal system. The proportion of adrenoxidase in the blood being very greatly increased, as shown by the tendency to hyperthermia and the anæmia (due to hæmolysis), there occur (1) hyperconstriction of all vessels owing to excessive metabolism in their muscular coats, and, as a result, hyperæmia of all capillaries (which are not provided with such a coat), including those of the serous membranes, especially those of the joints, and also, (2) as a result of hyperoxygenation of the pancreas and leucocytogenic tissues and hyperstimulation of the thyroid apparatus, an accumulation of autotoxic bodies in the blood-plasma, and effusion into the joints, serous membranes, glandular elements, etc. Hence the swelling, heat, severe pain, accumulation of fluid, and the inflammatory lesions, including erosion in the joints; hence also the marked predilection of serous membranes, the pericardium and endocardium, the myocardium, the tonsils, etc., to inflammation; hence, finally, the fibrous adhesions in the joints and around the neighboring structures which provoke ankylosis.

While the toxins of various bacteria, the staphylococcus citreus, the micrococcus lanceolatus, the gonococcus, may stimulate the test-organ sufficiently—especially in individuals in whom this organ is hypersensitive—to provoke acute rheumatism, it is caused in most cases by intermediate toxic waste-products which appear in the blood as a result of exposure to cold and the resulting hypocatabolism—the cellular trypsin failing, when the local temperature is below normal, to break down adequately wornout cell material.

Chronic rheumatism differs from the foregoing, in that the cause of the disease is inadequate catabolism of tissue wastes and excitation, by the toxic products formed, of the vasomotor center, while the pathogenesis of the joint lesions includes more or less increase of the vascular tension, as in the acute form.

Under these conditions, it is obvious that thyroid gland, by increasing the proteolytic activity of the blood, promotes destruction of the toxic wastes which underlie the disease.

Analyzing Lévi and de Rothschild's results from this viewpoint, the manner in which they were produced by their *small doses* becomes self-evident. Thus, increase of appetite was the first effect noted; this is a normal result, since the greater cellular activity and catabolism created a greater demand for foodstuffs. Increased heat production soon replaced the marked and constant chilliness from which the patient suffered—an effect due to the marked increase of oxidation the thyroid extract engendered throughout the body. The dose was increased to 1½ grains (0.1 Gm.) one day, then to 3 grains (0.2 Gm.) the next, this being continued ten days. After a period of rest of five days, 3 grains (0.2 Gm.) were again given daily. The pain became less—a fact due to decrease of the vascular tension, owing to increased destruction of the toxic wastes which excite the vasomotor center, thus causing constriction of all arteries. The sensory nerve-terminals being relieved of the hyperæmia which caused the pain, the latter became less marked in proportion. Closely connected with this beneficial action was the effect on the joints, viz.: the *hydrarthrosis became reduced.* Being also due to excessive vascular tension, it is plain that, by causing vasodilation in the manner just explained, thyroid extract caused the excess of fluid to leave the joints. The dose being still further increased until 7½ grains (0.5 Gm.) were taken daily, *emaciation* occurred —a well-known effect due to excessive catabolism provoked by large doses of thyroid extract.

Eleven months' treatment brought Léopold-Lévi and Rothschild's case back to a condition of comfort, the joints having resumed their shape and flexibility—with the exception of one knee, which remained ankylosed—owing doubtless to fibrosis, a condition beyond the reach of the remedy. This does not militate against its use, however; it simply shows that the treatment was resorted to too late to avoid irremediable organic lesions. Rheumatism with eczema and epilepsy in the child also disappeared under thyroid treatment in a case of Léopold-Lévi's.[44a]

In a case treated by Parhon and Papinian[45] thyroid extract produced, though the disease was of twenty-four years' standing, "a true regeneration." When 7½ grains (0.5 Gm.) in five divided doses daily had been given some time, palpitations, tachycardia, and arrhythmia appeared. On withdrawing the remedy these untoward effects ceased, but recurred as soon as its use was resumed. This affords additional evidence in support of a fact I have often urged, viz.: that the best effects of thyroid extract are obtained with *small* doses.

These results have been confirmed by other observers, notably by Combe, F. Claisse,[46] Souques,[47] Ménard,[48] Claisse and Vincent,[49] and more recently by Steele-Perkins[49a] and Wilson.[49b] Though thyroid products act very gradually, and require patience and careful watching, the method is a very promising one.

[44a] Léopold-Lévi: Soc. de Méd. Paris, Oct. 28, 1911.
[45] Parhon and Papinian: Presse méd., No. 1, p. 3, 1905.

ENURESIS.—In many instances this condition is due to general asthenia, and the muscular debility which attends this state carries along with it inability of the sphincters to perform their functions at all times, especially when, during sleep, general relaxation prevails. The influence of thyroid on general metabolism and nutrition and the resulting increase of functional power in all organs affect equally both the cystic and urethral sphincters and thus overcome the trouble.

According to Hertoghe,[50] nocturnal incontinence of urine in young children and adolescents is due to thyroid insufficiency. He observed a number of cases in which the use of thyroid extract was followed by improvement or cure. Children who suffer from incontinence are often undersized, and they present the infantile habitus in varying degrees—improperly placed teeth, nasopharyngeal adenoids, flat chests, and emaciated and slender extremities. Such patients—those in which thyroid gland will prove beneficial—are often flat-footed and their feet have an offensive odor, their gait is stiff, they suffer from pains in the thighs and from sciatica produced by the cold and moist surroundings in which they lie at night. The systematic examination of the urine in these cases shows an abundant deposition of the cells covering the free surface of the cystic mucosa. In children beyond 2 years of age Hertoghe gives 2 grains (0.13 Gm.) daily with 3 to 5 grains (0.2 to 0.33 Gm.) of potassium iodide and the bromides on retiring.

Additional signs are subnormal temperature, deficiency of hair in the external third of the eyebrows, as observed by Léopold-Lévi and de Rothschild; scaphoid scapulæ, delayed epiphysial development, as determined by the X-rays, and adenoid vegetations. In such cases removal of the latter fails to benefit the patient. Thus, Leonard Williams[51] reported a case of enuresis in a 9-year-old boy in which he tried removal of the adenoids. The operation made the boy much worse, however, and, believing that the removal of the adenoids deprived the boy of a necessary internal secretion, he then gave him thyroid extract, ½ grain (0.033 Gm.) twice daily. The result was instantaneous and complete, the boy no further wetting the bed. Twenty-four other cases were thus treated. Only one of these proved rebellious to the treatment. The essential point to remember is that thyroid gland is useful mainly in cases in which there exists hypothyroidia, some sign of which can always be discerned if it is at all present. Firth obtained marked improvement in 16 out of 28 cases with small doses, especially when the enuresis had persisted since birth.

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[46] Claisse: Klinisch-therapeutische Woch., S. 979, 1909.
[47] Souques: *Ibid.*, p. 1003, 1908.
[48] Ménard: Tribune médicale, No. 9, 1908; Rev. intern. med., p. 326, 1908.
[49] Claisse and Vincent: Münch. med. Woch., S. 1067, 1908.
[49a] Steele-Perkins: London Lancet, March 5, 1910.
[49b] Wilson: British Medical Journal, Dec. 10, 1910.
[50] Hertoghe: Bull. de l'Acad. Roy. de Méd. de Belgique, vol. xxi, No. 4, 1907.
[51] Williams; London Lancet, May 1, 1909.

Skin Diseases.—A prolonged trial of thyroid preparation in many diseases of the skin has led dermatologists to the conclusion that they were indicated in disorders due to deficient metabolism. As stated by Winfield, these include the erythematobulbous type, which includes *dermatitis herpetiformis*, and the psoro-eczematous type, to which belong *prurigo, psoriasis,* and *chronic eczema.*

This is explained by the action of thyroid products on oxidation and metabolism, as is well shown in the effects noted by Don: 1. Increased nutrition of the skin; hence its probable remedial action in ichthyotic conditions: an effect produced without any necessary abnormal perspiration. 2. Increased action of the cutaneous glands, accelerating excretion of waste-products, thus keeping the surface in a supple condition. 3. Regrowth of hair, as shown in myxœdema and some cases of general alopecia. 4. Increased activity of the epidermal layers, causing desquamation of unhealthy epidermis and reproduction of a new covering, as observed in ichthyosis, psoriasis, dry chronic eczema, and at times in myxœdema and cretinism.

Eason[52] reported several consecutive cases of *eczema in young children* successfully treated by thyroid. In the first case, 14 months old, the baby had suffered from eczema of the face for nearly a year. This had been entirely resistant to the usual applications and internal treatment; nor was hospital treatment more efficacious. Two and a half grains (0.165 Gm.) of a thyroid tablet was given daily. In a little more than one month the child was entirely well. His cure persisted for nearly a month, when the disease showed a tendency to recur. The second course of thyroid was followed by a permanent cure. The 4 other cases gave similar results. Moussous[53] observed 2 cases of eczematous seborrhœa successfully treated with thyroid. In the first case the scalp was normal at the end of two weeks; in the second in one month. Complete cure occurred in both cases, and has persisted.

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[52] Eason: Scottish Med. and Surg. Jour., May, 1908.
[51a] Firth: London Lancet, Dec. 2, 1911.

In *psoriasis* thyroid is harmful when the eruption is developing, but it sometimes acts with surprising efficacy in fully developed cases. The untoward effects observed by dermatologists, however, are in great part due to the fact that they use too large doses. Edelman[53a] recommends fairly large doses at first to supply the deficiency, then smaller doses to sustain the effect.

Pedrazzini[54] observed 5 cases of *scleroderma,* in 4 of which the thyroid was small and atrophied, while in the other the thyroid was large and hard. Thyroid treatment gave good results in the two in which it was applied, commencing with small and progressive doses. None of the patients presented signs of nervous changes suggesting atrophic origin, but everything confirmed the assumption of some connection between the cutaneous affection and the thyroid gland.

Thyroid has been tried in *lupus* by a number of observers. Though the results were contradictory, the bulk of the evidence indicates that it is worthy of more extensive trial. Owing to its influence on oxidation it enhances the nutrition of the skin and thus antagonizes the destructive process while promoting that of repair. As full doses have to be used during a prolonged period, the patient should be carefully watched. Thyroid has been tried in *leprosy,* but the results were not encouraging, though the remedy was pushed as far as safety would allow.

In a case of *hypertrophic rosacea* which has resisted all forms of treatment, Isadore Dyer, of New Orleans, used thyroid with, for local use, a salve containing resorcin ℈j; rose water ʒiv; lanolin ad ℥vj. After two months there was decided improvement, the skin being soft and normal to the touch and the color greatly improved. The patient was discharged cured after three months of thyroid medication.

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[53] Moussous: Archives de méd. des enfants, Mar., 1908.
[53a] Edelman: N. Y. Med. Jour., Mar. 9, 1918.
[54] Pedrazzini: Gaz. degli Ospedali, Aug. 1, 1909.

HÆMOPHILIA.—The various preparations of thyroid gland are extremely valuable in this dyscrasia, due to a deficiency of fibrin ferment in the blood. As this body, according to my researches, is mainly composed of the adrenal product, the increased functional activity of the adrenals, provoked by thyroid preparations administered, increases the blood's asset. The coagulation time in hæmophilia may be brought down from over ten minutes to three or four minutes in adults by 2-grain doses of the desiccated thyroid three times daily after meals. This is equally effective when operations become necessary.

Examples of the value of thyroid gland in a large proportion of cases of hæmophilia (we might say all, for the cases of recurrent hæmorrhage in which it fails are doubtless due to other causes) are now numerous in literature. Combemale,[55] for instance, cites the case of a woman who, for the preceding two years, had been suffering from hæmorrhages from the larynx. She was covered with purpuric spots, her gums bleeding. She was extremely weak and exhausted. Treatment with thyroid tablets was commenced; in ten days very marked and evident improvement; there was no purpura, no bleeding from the gums. In ten more days she had perfectly normal menses; all other hæmorrhages stopped. Scheffler[56] reported a case in which hæmophilic epistaxis was absolutely unaffected by ordinary therapeutic agents, and the epistaxis became so persistent and exhausting that permanent blocking of the nasal fossa was necessary. Treatment by thyroid extract exerted an immediate and beneficial effect, and was followed by cure. In three days the violent and persistent epistaxis had practically stopped. In six days, about 8 grains (0.53 Gm.) of thyroid gland having been given daily, the purpuric eruption ceased. A marked case in which the patient had become extremely anæmic was also reported as recovered by Rugh,[57] under the use of 5-grain (0.33 Gm.) doses three times daily.

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[55] Combemale: La médecine moderne, April 30, 1898.
[56] Scheffler: Archives de méd. et de pharm. militaire, March, 1901.
[57] Rugh: Annals of Surgery, May, 1907.

The value of thyroid in the preparation of hæmophilic cases for serious operations is well illustrated by W. J. Taylor[88] in 3 cases. The coagulation time was reduced with 3-grain (0.2 Gm.) doses three times daily from twelve minutes to three minutes, and the operations, including a nephrectomy, proved drier if anything than if they had been performed in a nonhæmophilic subject. The desiccated thyroid on the market, especially the standardized product, being stronger than that available in former years, 2 grains (0.12 Gm.) three times daily need not be exceeded even in these cases.

SURGICAL DISORDERS.—We have seen that in 1907 I pointed out that the thyroparathyroid secretion corresponded with what Sir A. E. Wright has termed opsonin. During the same year I urged that thyroid preparations, owing to their influence on oxidation and their power to increase both the opsonins and the germicidal activity of the blood, were indicated in the *early stage of tuberculosis*—mainly on account of the content of the tubercle bacillus in phosphorus, viz.: 55.23 per cent. of its ashes—a fact sustained clinically. Recently, Frugoni found not only that thyroid gland markedly raised the opsonic index of tuberculous animals, but also the active germicidal power of their blood. That this should entail in the surgical field marked progress in the treatment of all conditions due to tuberculosis is self-evident. In *hip-joint disease* and other *tubercular bone processes*, for example, thyroid is clearly indicated.

Besides its powerful stimulating action on the defensive functions, thyroid gland, as shown by Parhon, Macallum, and others, hastens calcium metabolism. This accounts for its value in *osteomyelitis* and *rhachitis*. We have striking evidence of its efficiency in the treatment of deficient metabolic activity in osseous tissue in the rapid growth of the skeleton in cretinism brought about with its aid. This has suggested its use in *delayed union in fractures*—where it is valuable only when more or less hypothyroidia exists—and accounts for its greater value for this purpose in the young than in the adult, its therapeutic action in this class of cases growing less as age advances.

Another indication for thyroid preparations, owing, however, mainly to their influence on general oxidation and metabolism, is in *hypothyroidia in operated subjects.* The presence of this condition, a larval and covert form of myxœdema indicated mainly by a tendency to obesity, cold hands and feet, dry skin, brittle hair perhaps, mental and physical torpor, rheumatic pains in the occiput and back usually treated unavailingly for rheumatism. Here deficient oxidation and metabolism entail a correspondingly deficient production of opsonin and other protective bodies. Such cases are readily infected, and their recovery after any operation, even sometimes after a trivial one, is unusually slow. A preparatory course of thyroid gland transforms completely such a case into one in which the chances of a successful result are as good as in a normal individual.

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[88] Taylor: Monthly Cyclopædia, July, 1905.

In *febrile infections* the thyroid gland is sometimes so active that it becomes enlarged and even quite painful. This is now recognized as a distinct effort to raise the protective process to adequate efficiency. In surgical diseases such as *septicæmia* and *erysipelas,* aid afforded to the gland by administering thyroid preparations has been found to curtail these diseases. It fulfills in a measure the rôle of antistreptococcic serum. This applies also to *suppurative processes* of all sorts due to general adynamia; the rapidity with which it produces beneficial effects in this class of disorders is sometimes striking. This applies also to suppurative processes situated in special organs, such as eye, ear, nose and throat, and the sinuses.

When the purpose is to increase the germicidal and antitoxic power of the blood, and also phagocytic activity, in any of the foregoing disorders, excepting pulmonary tuberculosis, the dose required must be somewhat larger, but not excessive. A condition similar to Wright's negative phase in vaccine therapy is readily brought about by excessive doses. In the laboratory such doses decrease instead of increasing the resistance of animals to infection. Again, as personal investigations have suggested, there is good ground for the belief that the so-called untoward effects observed under thyroid medication are closely allied to anaphylaxis. Two grains of the desiccated gland in tablet form slowly increased to 3 grains, three times a day, is the maximum that should be administered in the adult, and the patient should be carefully watched to forestall any undue action of the remedy. The best indication of any untoward effect, we have seen, is the pulse. Any considerable quickening or palpitation indicates that the remedy should be discontinued a few days, then resumed in smaller doses. Again, the preparations on the market vary in strength. The above dose refers to Armour's or Burroughs, Wellcome & Co.'s desiccated gland, which is standardized two-tenths of 1 per cent. of organic iodine.

In *cancer*, as will be shown in the second volume (see page 1389), thyroid gland is valuable in inoperable cases and after extirpation to prevent recurrence. As I emphasized in 1907, however, its best effects in the treatment of the disease are obtained when X-rays or radium and saline solution are employed concomitantly.

PARATHYROID ORGANOTHERAPY.

The physiology of the parathyroids was reviewed in the third chapter. We saw therein that the prevailing view was, that their secretion served to neutralize the toxic wastes which give rise to tetany, and that it influenced calcium metabolism. I defended therein Gley's opinion, that it supplemented the function of the thyroid gland, and, moreover, my own previously advanced conclusion, that thus combined the thyroparathyroid secretion increased the germicidal and antitoxic power of the blood by endowing the albuminous portion of the hæmoglobin with sensitizing properties, and that, as such, it was the blood constituent Sir A. E. Wright had termed "opsonin." Just what rôle the parathyroids fill in the dual process cannot at present be determined, but the fact that, as shown by Gley, the proportion of iodine in them is much greater than in the thyroid proper suggests that it supplies the most active component of the compound secretion, that part of it which has to do with the sensitizing or opsonic action. This is due, we have seen, to the iodine itself, owing to the peculiar property it possesses of increasing the inflammability of phosphorus.

From the standpoint of organotherapy, it is this property that we must bear in mind. We must look upon parathyroid glandules or adequate preparations of these organs as the essence, so to say, of the whole thyroid apparatus, in so far as its antitoxic properties and its rôle in calcium metabolism are concerned. This agrees with the teachings of experimental evidence, particularly that afforded by Jeandelize,[59] which have shown that the secretory product of the thyroid gland proper is more concerned with the processes of general nutrition and development than with the auto-protective function.

The manner in which the parathyroids affect the organism and the influence of parathyroid gland as a remedy seem to me best illustrated in the symptomatology and treatment of the first condition analyzed on the opposite page (741) under the title of "hypoparathyroid tetany."

As to the preparations available, Berkeley[60] claims that the only available glands are those from the bullock, and these are hard to find anatomically—as I know from experience—and expensive. He no longer uses the preparations obtainable on the market, and employs only glands obtained fresh at the abattoirs under his own supervision. He found that the gland could be administered either as fresh gland, preserved gland or nucleoproteid solution. In the author's words:—

"The *fresh gland* is given in the simplest manner possible, minced and eaten in a bread-and-butter sandwich. The dose is from 5 to 8 glands per day. This method is, of course, available only for patients living near a large abattoir where someone has been taught how to find the material.

"In the matter of *preserving the gland*, the essential thing is to get the tissue finely divided and in intimate contact with the preservative. The glands are trimmed with sterile instruments, dried between folds of sterile gauze, and rubbed up patiently in a mortar with an excess of milk-sugar and a small percentage of boric acid to a fine, dry powder. A trace of oil of peppermint is usually added. Prepared in this way, dispensed in capsules, and kept on ice, they keep from four to six weeks. The dose is 5 to 8 per day, each capsule corresponding to ½ a grain [0.033 Gm.] of fresh gland. They are now for sale in several New York pharmacies.

"The *nucleoproteid* (S. B. Beebe's method) is extracted as follows: The glands are thoroughly triturated—a few at a time—in a mortar with laboratory sand. The triturate is made distinctly alkaline with lithium carbonate solution and extracted with normal salt solution in excess. The process of extraction takes twenty-four hours. The container is frequently shaken, and between whiles placed on ice. The solution is now filtered, and finally acidulated with a few drops of 10 per cent. acetic acid. The nucleoproteid settles to the bottom as a voluminous, flocculent, white precipitate. In two hours the overlying fluid, which is now clear, and contains no albumin at all, and only a little globulin, is decanted, and the precipitate is redissolved by adding a little more lithium carbonate, till a slight alkaline reaction is again obtained. This concentrated solution may be diluted to any desired strength. I usually dilute till the number of c.c. is equal to the original number of fresh glands used. The dose of the preparation is about 20 drops [1.23 c.c.] per day. It is readily preserved with a little chloroform or thyroid, and if kept on ice stays effective about half as long as glycerinated vaccine virus, or diphtheria antitoxin. To make it suitable for hypodermic use, it should be more concentrated than as described above, carefully standardized, run through a Chamberland filter, and put up in sealed tubes."

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[59] Jeandelize: "Insuffisance Thyroïdienne et Parathyroïdienne," Nancy, 1902.
[60] Berkeley: Old Dominion Journal, April, 1909.

Proceeding with the consideration of the few disorders in which parathyroid has been used, it was deemed best to treat the first of these, hypoparathyroid tetany, in the same manner as other diseases of the ductless glands reviewed in the earlier chapters of this volume, owing to the important position this disorder now occupies in the clinical, and to the fact that it is scantily, if at all, treated in works on surgery.

HYPOPARATHYROID TETANY. (Tetania parathyreopriva; Parathyroid Tetany; Hypoparathyrosis; Cachexia Parathyreopriva; Status Parathyreoprivus or Hypoparathyreoprivus.)

Tetany due to hypoparathyroidia occurs as a result of any condition which temporarily or permanently arrests the functions of the parathyroid glandules. The form most generally recognized at the present time is that variously known as tetania parathyreopriva, cachexia parathyreopriva, status parathyreoprivus, which follows removal of the parathyroids along with the thyroid in goiter and other growths of this gland—a subject already treated on page 174. The second form is due to organic lesions, such as tuberculosis, interstitial hæmorrhages, inflammatory lesions during infections, etc., of the parathyroids sufficient to greatly impair their secretory activity. These organs being the source, with the thyroid, of one of the auto-defensive constituents of the blood, as previously shown, their functional arrest allows those poisons—toxic waste-products in the present connection—to accumulate in the blood and to provoke tetany and even, in very severe cases, the clonic convulsions of epilepsy.[61] In its general terms, therefore, hypoparathyroid tetany may be defined as follows:—

Hypoparathyroid tetany is a disorder due to impairment or arrest of the secretory activity of the parathyroids, characterized by more or less severe spasms or convulsions, the result in turn of accumulation in the blood of toxic waste-products, which it is one of the functions of the parathyroid secretion, as the opsonic constituent of thyroiodase, and along with other antitoxic constituents of the blood, to convert into benign, eliminable end-products.

SYMPTOMATOLOGY. *Post-operative Parathyroid Tetany.*—The symptomatology of this disorder may vary considerably in intensity and in the time and manner in which it appears. In most cases, however, the tetany begins by a sensation of stiffness around the mouth with twitching of the facial muscles and tingling or formication. This is soon followed by stiffening of the masseter muscles and fibrillary contractions or rigidity of the tongue—which causes difficulty of speech and deglutition—and finally locking of the jaws, as in true tetanus. This is often accompanied by trembling of the eyelids. The thumbs and then the hands are thrown backward, *i.e.*, in marked extension, the fingers assuming either the claw-like or "*main en griffe*" shape, or, with two fingers, the index and medius, extended, the "obstetric position." There is at the same time flexure of the forearms, often complicated with more or less severe pains in the flexed muscles. The feet are also cramped, often in the equinovarus position, the pain being then located in the calves. In severe cases opisthotonos may occur, the body being supported only on the head, shoulders, buttocks, and heels. There is a feeling of intense tightness around the heart. The respiratory muscles, thoracic and pulmonary, being likewise contracted spasmodically, respiration becomes difficult, sufficiently so at times to provoke intense dyspnœa and cyanosis. There may also be marked strabismus, dilatation of the pupils, frothing at the mouth, and clonic movements similar to those observed in true epilepsy.

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[61] See pp. 1429 and 1437, vol. ii, for the pathogenesis of tetany and tetanus.

The pulse becomes rapid and weak and sometimes irregular during the attacks, and the temperature is raised. As explained in the article on tetany in the second volume, the latter symptom is partly due to the presence of an excess of adrenoxidase in the blood and the increased oxidation this entails—the adrenal center being stimulated by the toxic wastes accumulated in the blood—and partly to the rise of blood-pressure, which causes blood to be driven from the deeper vessels to the periphery, and then to congest the cutaneous capillaries. When marked this phenomenon also causes burning sensation over the entire body.

Tetany may occur almost any time after the operation, the period of onset varying greatly. As a rule, however, the first signs occur the third or fourth day after the operation, the intervening period representing doubtless that during which the supply of thyroiodase is being exhausted. The frequency of the paroxysms also varies in different cases, from one to many a day, according in a measure to the diet and amount of exercise to which the patient is subjected. In some cases the parathyroids are only injured during the operation, and their recovery ends the tetany.

Non-operative Hypoparathyroid Tetany.—The symptoms of this condition do not vary from those just described, though they are less marked. In some cases, in fact, they hardly exceed in intensity those produced by strychnine in full therapeutic doses, when the physiological limit of the drug has been reached. Here the parathyroids are able to carry on their functions only in part, the lesions produced in them by local disease, tuberculosis, interstitial hæmorrhage, etc., having left perhaps one or more of the organs or a part of their parenchyma intact. The thyroiodase formed under these circumstances being deficient in the constituent which endows it with its antitoxic properties, it allows the spasmogenic poisons to accumulate in the blood very gradually, and in relatively small quantity as compared to that which invades the blood when all the parathyroids are destroyed by operation or disease.

In these mild cases, the identity of the disorder present may be determined by various signs: Trousseau's, tapping or pressure upon large nerve-trunks to elicit muscular contractions; Chvostek's, the production of spasm of the facial muscles by tapping over the facial nerve close to the parotid or over the muscle itself; Hoffmann's, the percussion of sensory nerves to demonstrate hyperæsthesia; Erb's, hyperæsthesia of the nerves under electric stimulation. All these phenomena are explained by the fact that, as previously urged (see also the articles on Tetany, page 1429, and Tetanus, page 1437, in the second volume), the spasmogenic toxic excites the vaso-motor center, producing thereby contraction of all vessels and driving the blood from the great deeper channels to the periphery. All peripheral muscles and nerves being rendered hyperæmic, they become correspondingly sensitive to irritation and stimulation.

Careful differential diagnosis is necessary in these cases, since tetany is also produced, irrespective of any parathyroid disorder (though the parathyroids may show active hyperplasia, as observed by MacCallum, in a fatal case of gastric dilatation), by many other disorders: gastric and intestinal, pregnancy and lactation, uræmia, violent excitement and exertion, etc.—all conditions in which the blood becomes laden with toxic substances. Infectious diseases are also prominent causes of tetany, but probably in part through the lesions of the parathyroids they sometimes produce.

TREATMENT.—Tetany should always be borne in mind when any operative measure involving the thyroid is to be resorted to, since post-operative tetany would never occur if the parathyroids were always spared. Referring the reader to works on surgery for details, it may be mentioned here that every effort should be made to protect not only the parathyroids themselves by preserving the posterior capsule of the thyroid, upon which they lie, but also to so ligate the thyroid vessels with which they are connected as to provide for uninterrupted circulation through them. I would suggest also that their lymphatic connections be as much as possible spared, since, as we have seen, the parathyroid product reaches the venous circulation through their intermediary.

Important in this connection also is the selection of the portion of the thyroid that is to be removed. Kocher, according to Erdheim,[62] who generally removes the central part of the gland, has "hardly ever had a loss from cachexia strumipriva or tetany." Again, complete removal of the thyroid itself is never justified, and as large a portion of the organ as possible should be left to insure the continuation of the function it fulfills in conjunction with the parathyroids. If the parathyroids are accidentally removed with the thyroid, which a careful examination of the extirpated organ should enable the surgeon to determine, they should at once be dissected out and implanted into the cervical tissues, selecting as much as possible a region rich in blood-vessels.

In some cases, operated with due care, the parathyroids left *in situ* may be injured, or suffer, perhaps, from shock. Under these conditions, mild tetanic symptoms may occur temporarily. In 500 thyroidectomies performed by von Eiselsberg[63] in about seven years, 15 showed Chvostek's sign, but it disappeared without treatment in a few days. In 10 cases there was well-developed tetany, with one death, total removal of the parathyroids in the latter being probable.

W. H. Brown[64] rightly criticises the indifferent attitude of some surgeons concerning the importance of the parathyroids to the organism, and sustains his position by an extremely severe case of tetany, saved only by the implantation of the thyroid with its parathyroids obtained from a small monkey, and, one month later, of three parathyroids and a piece of thyroid the size of a small walnut, obtained one-half hour after death from the body of a man who had died of Bright's disease and uræmia. These tissues placed at once in normal saline solution at 32° F. (0° C.) were implanted successfully within an hour, the simian thyroid beneath the patient's sterno-mastoid, and the human thyroid and parathyroid beneath her left rectus abdominis, under chloroform anæsthesia. Danielsen[65] also transplanted human parathyroids in a critical case with a successful result, and mentions 3 recorded cases.

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[62] Erdheim: Brit. Med. Jour., July 21, p. 167, 1906.
[63] Von Eiselsberg: Centralbl. f. Chir., Nu. 21, 1909.
[64] Brown: Annals of Surgery, March, 1911.
[65] Danielsen: Beitrage z. klin. Chir., Bd. xxxvii, p. 996, 1910.

An essential feature of parathyroid implantation is that the improvement may prove temporary only, *i.e.*, until, probably, the secretion the organ happens to contain is exhausted. This may last a couple of weeks and the symptoms return. It is only when the implanted organ assumes its normal functions *in situ* that cure occurs if the secretion produced is sufficient. Halsted's[66] valuable researches on the subject should be read by all operators in this class of cases.

That the oral use of parathyroid gland is of value in parathyroid tetany has been shown by MacCallum, Vassale, and others, though the first-named observer found that large quantities were necessary. Berkeley refers to other well-known observers, James, Putnam, and Halsted, as having obtained favorable results. In 2 cases recently reported by Bircher,[67] thyroid gland had first been tried, but without effect; parathyroid, however, caused prompt recovery.

An emulsion of fresh parathyroids may be given subcutaneously. Branham[68] reported a case thus treated successfully. Five fresh beef parathyroids were placed in a 1:1000 solution of bichloride of mercury and allowed to soak about ten minutes. The glands were cut, under strict asepsis, into 5 pieces under physiological salt solution. These pieces were placed in a mortar and ground into a homogeneous mass, 400 c.c. of sterile salt solution being poured into the mortar. This was then filtered through a sterile gauze and given as salt transfusion into the patient's breast. The oral use of thyroid and parathyroid extracts and the feeding of raw parathyroids had proved entirely useless. The recovery in this case, however, seems to me to be due to the fact that only one parathyroid was totally removed, and the three others only partly so, the remaining segments having eventually resumed their secretory activity. The injected emulsion thus acted as a palliative pending the functional recovery of what had been left of the organs. In Brown's case in which the parathyroids were removed, the benefit obtained from the emulsion lasted eleven days, and was then followed by violent tetany. Bircher's[69] 2 cases, also treated successfully with thyroid tablets, were probably of the same kind. Kocher[69a] obtained recoveries "by energetically pushing the thyroid extract and iodothyrin in large doses." Biedl[69b] urges that it should always be tried.

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[66] Halsted: Amer. Jour. Med. Sci., vol. cxxxiv, No. 1, July, 1907, and Annals of Surgery, vol. xlvi, p. 489, 1907.

[67] Bircher: Medizinische Klinik, Oct. 30, 1910.

[68] Branham: Amer. Jour. Med. Sci., vol. xlviii, p. 161, 1908.

On the whole, what evidence there is tends to show that implantation of fresh glands should alone be depended on for a cure when the parathyroids have been destroyed.

Calcium lactate has been found efficacious by MacCallum and Voegtlin[70] and others. It may be given in 10-grain (0.66 Gm.) doses every hour or two, or in larger doses in saline solution per rectum, or in emergency cases, intravenously, 4 grammes (1 drachm) being given in 100 c.c. (25 drachms) of salt solution, as recommended by Winternitz,[71] in a case of non-operative tetany. In Brown's case, however, calcium lactate, given orally, proved useless, as did all organic agents, including parathyroids. Large injections of normal saline solution are used by Gomez[71a] and copious hypodermoclysis by Chvostek[71b] with washing of the stomach, stopping food for a couple of days.

The diet should receive considerable attention, and all substances rich in nucleins, including meats, should be strictly avoided, to reduce to a minimum the formation of spasmogenic wastes. A milk diet, farinaceous foods, and the free use of water to facilitate the elimination of what toxic wastes are formed are most useful in this connection. Exercise of any kind is also harmful, owing to the formation of muscular wastes that it entails. Rest in bed, or in an armchair, tends greatly to reduce the number and severity of the spasms.

PARALYSIS AGITANS.—This is a particularly interesting syndrome from the standpoint of physiology, for it clearly sustains the view that the thyroid and parathyroids are functionally united. Indeed, while Möbius, in 1883, found paralysis agitans associated with exophthalmic goiter, Lundborg, in 1891, met it in connection with myxœdema, the autopsy showing atrophy of the thyroid. These facts led both Möbius and Lundborg to connect the disease with the thyroid gland.

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[69] Bircher: Medicinische Klinik, Oct. 30, 1910.
[69a] Kocher: Quoted by Biedl, "Internal Secretory Organs," p. 50, 1913.
[69b] Biedl: *Ibid.*
[70] MacCallum and Voegtlin: Johns Hopkins Hosp. Bull., vol. xix, p. 91, 1908.
[71] Winternitz: *Ibid.*, vol. xx, p. 269, 1909.
[71a] Gomez: Riforma Medica, Jan. 23, 1900.
[71b] Chvostek: Deut. med. Woch., May 20, 1909.

Various other phenomena, such as chronic rheumatism, arthritis, scleroderma, a brawny, or yellow-brown, pigmentation, hypothermia, etc., met with in cases of hypothyroidia, are also observed in paralysis agitans. In a case of mine the mask-like face of the latter disease recalled clearly that of an incipient case of myxœdema; Fraenkel had already observed myxœdematous areas. Parhon and Golstein[72] found in the thyroid proper of a woman who had died of paralysis agitans what they term "manifest macroscopical and microscopical lesions"; Castelvi[73] found marked atrophic lesions in the thyroid gland in two instances, though Pasquier found none.

Conversely, many cases of paralysis agitans may suffer from the sensations of heat with cutaneous rise of temperature, and the abundant sweating commonly observed in exophthalmic goiter. The most suggestive case in this connection, however, is one reported by A. Gordon,[74] in which the characteristic attitude of paralysis agitans, the stiffness and fixation, the mask face and absence of expression, the propulsive movement and the tremor, coincided with goiter, some degree of exophthalmus, tachycardia, dyspnœa, and Graefe's sign of exophthalmic goiter.

There is ground, therefore, for the hypothesis that the genesis of paralysis agitans is in some way related to the thyroid apparatus. Yet. a suggestive feature of the problem is, that thyroid preparations are useless in these cases, as many observers, including myself, have ascertained. Again, the fact that, while the main phenomena of exophthalmic goiter are distinguishable in certain cases, in others those of myxœdema occur, serves further to obscure the problem. Moreover, while R. L. Thompson[75] examined fruitlessly the parathyroid of 9 cases in which death had been due to paralysis agitans for lesions, others, including Berkeley[76] and Allen J. Smith, referred to in paper by Camp,[77] found lesions in these glandules. Indeed, Lundborg[78] suggested, in 1904, that paralysis agitans was specifically the syndrome of hyperparathyroidia, a view to which Berkeley[79] was also led independently, in so far as disease of the parathyroids is concerned.

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[72] Parhon and Golstein: "Les Sécrétions Internes," p. 218; 1909.
[73] Castelvi: Rivista de medicina y cirugia practicas, 1904.
[74] Gordon: Proceedings of the Philadelphia County Medical Society, Sept. 14, 1904.
[75] Thompson: Journal of Medical Research, Dec., 1908.
[76] Berkeley: Old Dominion Journal, April, 1908.
[77] Camp: Jour. of the Amer. Med. Assoc., April 13, 1907.

That the latter view is based on good ground is suggested by the fact that, while, as stated above, thyroid preparations are useless in paralysis agitans, active preparations of parathyroid favorably influence the disease. Moreover, their favorable action harmonizes with two established facts: that the parathyroids produce a powerful antitoxic substance, and that the pathogenic element of the disease is a long-recognized toxæmia. That symptoms of exophthalmic goiter and of myxœdema occur, does not weaken this position if the thyroid and parathyroids are united functionally. Nor does the presence of these two antagonistic disorders militate against the parathyroid theory, since we have seen that exophthalmic goiter lapses, if the patient lives long enough, into a myxœdematous state. Nor need we even deem Thompson's failure to find lesions in the parathyroids as defeating the Lundborg-Berkeley theory, for the functions of the parathyroids may be inhibited precisely as are those of the adrenals and thyroid, by lesions along the paths of the nerves through which their functions are governed. Hence the cases on record in which the causative lesion was found in various parts of the cerebrospinal system.

Suggestive also is the beneficial action of parathyroid. Berkeley[80] first employed commercial preparations; while good results were obtained in some instances, they often proved unreliable. He then used properly identified gland rubbed up fresh with milk-sugar into a dry powder, but found this also unstable. Subsequently he used the nucleoproteid solution referred to under the preceding heading as prepared by Beebe's method, and preserved with a few drops in the bottom of the container. This raised the therapeutic value of the product, but it was found to precipitate readily, and that it failed to bear prolonged transportation. His latest process is the following: The nucleoproteid extraction process (Beebe's method) is adhered to generally, but all the preliminary steps are hurried, and the precipitated nucleoproteid is not redissolved, but quickly dried in a draught of cold air; so that within eight or ten hours after the warm glands leave the bullock a minute amount of smooth yellow powder is obtained which stands physiologic tests admirably, is stable, easily handled, and does not require a freezing temperature (though for safety's sake it is recommended to keep it on ice). The powder is rubbed up with milk-sugar as a menstruum, and is placed in sealed containers.

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[78] Lundborg: Deutsch. Zeitschrift für Nervenheilkunde, "27," 1904.

[79] Berkeley: Medical News, Dec., 1905.

[80] Berkeley: Medical Record, Dec. 17, 1910.

A large proportion of the patients slowly respond to the treatment, though in about 25 per cent. the response is only temporary and imperfect. The rest showed progressive benefit during the entire period of treatment. The dose of nucleoproteid, as previously stated, is about 20 drops (1.23 c.c.) per day, while that of the glandules proper is 5 to 8 per day. The preserved gland is also given in capsules containing each the equivalent of ½ grain (0.033 Gm.) of fresh gland, 5 to 7 of these being given daily. Parhon and Urechia[61] and Delille,[62] and others, have also reported considerable improvement, though the rigidity did not seem to be influenced.

ADRENAL OPOTHERAPY.

The now discredited view that adrenal preparations cause a rise of blood-pressure, besides increasing the vascular tone has greatly limited the intelligent use of these agents, though their empirical employment has somewhat compensated for this, and clinical applications have thus been discovered which the limited field of laboratory experimentation would never have brought to light. As we have seen, however, the adrenals are endowed with far more important functions, from my viewpoint: (1) their secretion takes up the oxygen of the air in the pulmonary alveoli and carries this gas to the tissue as constituent of the hæmoglobin; (2) it sustains, as such, oxidation, *i.e.*, metabolism, of the tissues (the latter having been sensitized for this purpose, we have seen, by the thyroiodase).

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[61] Parhon and Urechia: Soc. de Neurol., Nov. 7, 1907.

[62] Delille: L'hypophyse et la médication hypophysaire, p. 126, 1909.

While this conception sustains the present interpretation, it accounts for clinical phenomena which had not previously been explained, witnessed in the use of adrenal preparations. It shows, we have seen, that the rise of temperature noted by Morel, Lépine and the concomitant rise of temperature and increased metabolism noted by Oliver and Schäfer are due to increased oxidation. It accounts also for the rise of blood-pressure after prolonged use or very large doses, since increased metabolic activity—excited directly by the adrenal principle besides that due to general oxidation—of the muscular coats of vessels causes contraction and elevation of the blood-pressure. The increased power of the heart is the obvious outcome of increased metabolism in the myocardium, precisely as it is in the vascular muscles, while the slowing of its action is due to the greater diastolic expansion that attends increased functional vigor.

The preparation most used is the *glandulæ suprarenales siccæ*, or dried adrenal gland, of the U. S. P. It is best given in capsules in doses of from 2 to 4 grains (0.13 to 0.26 Gm.).

Adrenalin, except in 15-minim (1 Gm.) doses (Josué, 1917) is unreliable given orally, being often oxidized in the stomach and intestines, and rendered inert. It is absorbed from the colon.

Adrenalin may be injected subcutaneously in 10- to 20-minim (0.62 to 1.23 c.c.) doses in small (1 to 2 drachms—4 to 8 Gm.) or large (1 to 2 pints—500 to 1000 Gm.) quantities of warm saline solution, the smaller quantity of the latter being preferable when repeated doses are necessary, absorption being very slow. It causes pain and, sometimes, general pallor when the injections are repeated, owing to contraction of the arterioles. The addition of 0.01 gram ($^1/_6$ gr.) of novocaine to the solution prevents the pain. Injections are contraindicated in infants and cardiac disorders.

When prompt results must be obtained, as in the treatment of shock, cardiac failure, etc., the intravenous method is preferable, injecting slowly 10 to 20 drops (0.62 to 1.23 c.c.) in a pint or quart of hot (108° F.—42° C.) saline solution. Or, 5 to 10 minims (0.3 to 0.6 Gm.) in 2 drachms (8 Gm.) of saline solution may be injected drop by drop into a vein, using a hypodermic syringe in an emergency.

The local application of an adrenal principle, adrenalin, epinephrin, etc., causes such marked contraction of the vessels that their lumina, when applied over small vessels, may become obliterated, thus arresting totally the flow of blood. The tissues become very pale, therefore, and even blanched, owing to the active metabolic activity set up in the vascular walls, and particularly their muscular elements.

The disorders in which adrenal preparations are indicated are numerous; but the majority of those in which they are of greatest value have already been considered, viz., *Addison's disease* (page 97) and *terminal hypoadrenia* (page 109), which in itself includes practically all febrile infections. A few others, however, may be considered here.

SURGICAL DISEASES.—Laboratory and clinical experience tend increasingly to show that man is more susceptible to the action of adrenalin than animals. While a subcutaneous injection of 1 drachm (4 c.c.) of a 1:1000 solution will hardly affect a rabbit, one-third of that quantity has produced untoward effects in normal as well as in tuberculous subjects (Souques and Morel), *e.g.*, vertigo, nausea, vomiting, severe pain under the sternum similar to that of angina pectoris, and a feeling of constriction about the chest, a rapid pulse, dyspnœa, cold sweats, and coldness of the extremities. Hypodermic doses of $^1/_{120}$ grain (0.00055 Gm.), however, are well borne. Intoxication may follow the use of adrenalin when injected into cavities such as the vagina, the rectum, the urethra, when the mucous membrane is abraded, lacerated, or denuded, thus rendering its absorption possible. The urethra seems to be particularly sensitive in this connection, the passage of bougies for stricture having caused poisoning in a number of cases. According to Braun,[88] the toxicity of epinephrin or other adrenal principles varies with the individual, but, in all, the danger lies in the use of concentrated solutions. He employs a solution of 0.64 Gm. (10 grains) of suprarenin borate in 100 c.c. (25 drachms) of 0.5 per cent. novocaine made up fresh from tablets for each operation; 125 c.c. (31 drachms) of this solution can be used without danger.

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[88] Braun: Zeit. f. Gyn.; Amer. Jour. of Obstet., 1909.

Local applications may also be followed by untoward effects in the tissues to which adrenalin solutions are applied. Repeated applications, especially with the atomizer, of anything but weak solutions (1:10,000) to the nasal cavities or pharynx may give rise to œdema of the nasal mucosa, the uvula, tonsils, or pillars of the fauces. This is ascribed by most writers to "violent vasomotor constriction of the blood-vessels" and the resulting "venous stagnation," but it is in reality a secondary result of these effects, *i.e.*, paresis of the arterioles and œdema of the tissues. In some instances they cause persistent sneezing and acute coryza accompanied at times by severe pain in the upper portion of the nasal cavities. Some cases have been reported in which even sloughing and gangrene of the mucosa occurred. Elderly subjects are prone to this complication, according to Neugebauer. Post-operative hæmorrhages are not infrequently noticed after the use of adrenalin, owing to relaxation of the severed vessels. In the larynx, adrenalin solutions cause an uncomfortable dryness by interfering with the formation of lubricating mucus. This is especially distressing to singers. In the eye their use in scleritis and other disorders may be followed by severe iritis. Instillations of a 1:1000 solution in the Eustachian tubes have given rise to violent pain in the middle ear, which was renewed whenever the remedy was thus administered. The use of adrenalin solutions in the form of spray, at least, is contraindicated in infections, owing to the danger of facilitating the entrance of pathogenic germs into the sinuses.

The toxic effects produced, however, are readily accounted for by the functions in oxidation, metabolism, and nutrition I attribute to the adrenal secretion. Tracing the course of events from start to finish, we have at first the effects of excessive metabolism in all tissues: in the cerebro-spinal system, excitement; in the muscles, tremor; in the kidneys, polyuria; in the myocardium, violent contractions (palpitations); in the muscular coats of the vascular system, a marked rise of the blood-pressure. The latter in turn aggravates the process by causing congestion and engorgement of the capillaries (which are not, like the arteries, provided with a muscular coat) of all organs, including the lungs, causing œdema of these structures and dyspnœa. As the contraction of the arteries proceeds, the aorta has to bear the brunt of the centrifugal pressure, giving rise to marked substernal pain. When it becomes such that the arterioles obstruct the circulation the lethal phenomena are initiated: the pulmonary circulation being impeded, oxygenation fails to occur; asphyxia follows, and, the myocardium receiving too little blood to sustain its contractile power, the heart, already hampered by the pulmonary congestion, ceases to beat.

After local applications the morbid effects are all the result of the action of the adrenal principle upon the vessels. The dryness caused by solutions sprayed into the larynx is due to deficiency of blood supplied to the acini and the resulting inhibition of their function. If this is kept up by repeated applications, the tissues, no longer nourished, may slough off, as has been noticed in the upper respiratory tract of aged subjects. The œdema observed in this location is not active, as it is in the lungs, but passive, *i.e.*, due to exaggerated relaxation of the vessels after the intense constriction to which the drug had subjected them. This applies equally well to post-operative hæmorrhage, and to the severe pain (due to passive congestion) in the middle ear after instillations in the Eustachian orifice.

Shock and Collapse.—The familiar influence of adrenal preparations on the blood-pressure and the rôle in tissue oxygenation I ascribe to them afford a self-evident explanation of the excellent action they have shown in the treatment of this condition, since they meet at once the two main morbid factors: low cardio-vascular tension and depression of the vital process. The latter effect is shown by the increase of body heat noted by Reichert, Lépine, Morel, and others.

Kinnaman, in a comprehensive study of the temperature relationship to shock, concluded that as shock increased in severity the most uniform and progressive factor was the fall in temperature. He states that "in one series [of cases] the fall in temperature was the sole cause of shock." The results of Crile with adrenalin in salt solution given very slowly and gradually for a considerable time thus find a normal explanation in my interpretation of the rôle of the adrenal secretion. He resuscitated animals in this manner—with simultaneous artificial respiration—fifteen minutes after all signs of life had ceased, and was able to keep a decapitated dog alive over ten hours by this same procedure. That it was because the adrenal secretion is able to incite and sustain tissue metabolism, *i.e.*, the vital process itself, that such results were obtained seems obvious.

This applies not only to shock, but also to *surgical heart-failure, collapse* from hæmorrhage, *asphyxia*, and *submersion*. The adrenal principle (suprarenalin, adrenalin, etc.) promotes energetically, as a catalyzer and constituent of the hæmoglobin, the intake of oxygen and its utilization by the tissue-cells, including the muscular elements of the cardio-vascular system, and thus causes them to resume their vital activity. It should be very slowly administered intravenously, 5 minims (0.31 c.c.) of the 1000-solution to the pint of warm (105° F.—40.5° C.) saline solution. In urgent cases, 10 drops (0.62 c.c.) of supracapsulin or adrenalin in 1 drachm of saline solution can be used instead, and repeated at intervals until the heart responds. Artificial respiration hastens its effects.

The same remarks apply to the untoward effects of chloroform, which are also due to circulatory failure, with partial suspension of the vital process in the tissue-cells. Here a relatively large dose must be used, 30 minims (2 Gm.) of epinephrin, supracapsulin, or adrenalin in a pint of warm (108° F.—42.5° C.) saline solution intravenously. If injected very gradually it will excite the cardiac muscle by a direct action upon it before reaching the lungs, and cause it to resume its contractions. Kothe[84] has used this method successfully in 5 cases of cardiac failure following spinal anæsthesia. Too rapid injection causes cramp of the cardiac muscle and holds it in systole. Dupont[84a] found that $^1/_{120}$ grain (0.0005 Gm.) in 1 pint (500 Gm.) saline solution very effective in shock.

The simultaneous use of $^1/_{100}$ grain (0.00066 Gm.) of atropine, hypodermically, aids materially the resuscitation by causing the arterioles to resume their functional tone, and thus to re-establish the *vis-a-tergo* motion of the blood in the capillary system. The physical methods, rhythmical traction of the tongue, suspension, etc., must, of course, not be neglected.

Hæmorrhage.—In hæmorrhage from the pharyngeal, œsophageal, gastric, or intestinal mucous membrane, the mastication of adrenal substance, or the use of powdered adrenal substance in 5-grain (0.33 Gm.) capsules, arrests the flow, by causing active metabolism in the muscular elements of the arterioles of the mucosa and constriction of these vessels—the characteristic local action of the adrenal principle.

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[84] Kothe: Therapie der Gegenwart, p. 95, 1907.
[84a] Dupont: Arch. de méd. et de pharm. milit., lxiv, 542, 1915.

Its use in intestinal hæmorrhage was studied with considerable care recently by C. J. Wiggers.[85] His conclusions were as follows: 1. Large doses of adrenalin (0.05 to 0.1 mg.) cause a short preliminary increase in hæmorrhage, followed quickly by a decrease or cessation of bleeding. On account of the great preliminary loss of blood they are always contraindicated. 2. Small doses of adrenalin (0.01 to 0.025 mg.) cause little or no preliminary increase, but shorten the course of hæmorrhage. As they save the red blood-cells in every way they are therapeutically desirable. 3. The method of introducing adrenalin determines the effect of blood-pressure and hæmorrhage. No results are obtained by subcutaneous administration. By continuous intravenous injection of weak solutions a slight elevation of pressure can be maintained and hæmorrhage simultaneously checked. This can also be accomplished by intramuscular injection. 4. Adrenalin is not indicated in all intestinal hæmorrhages. The condition of the blood-pressure is the criterion for its use. In hæmorrhages of short duration when the pressure has not fallen to any extent, a judicious use of nitrites proves of more benefit than adrenalin. When the bleeding has been profuse, however, and a low pressure already exists, it becomes vital that hæmorrhage should be checked without further reduction of pressure. Adrenalin finds its use in this field. 5. The use of adrenalin should always be closely followed by blood-pressure observations. A dose sure to be below the safety limit should first be tried, and the pressure carefully estimated. If no rise occurs, gradually increasing doses may be injected until a slight elevation of pressure is present.

TOXÆMIAS.—It was noted long ago by Abelous and Langlois, Charrin, Oppenheim, and others, that adrenal extracts antagonized certain toxins and other poisons. This is due to the participation of the adrenals in general immunity which I pointed out as far back as 1903, the specific action carried on by their secretion being that of amboceptor. Goldsieher[85a] noted a marked diminution of adrenalin in the adrenals of subjects in which death had been due to an infection: pneumonia, puerperal meningitis, etc., thus showing that in all such processes there is abnormal activity of the organs, *i.e.*, an extraordinary output of adrenal secretion. Many clinicians are now using adrenal preparations to compensate for this loss. (See Terminal Hypoadrenia, page 109).

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[85] Wiggers: Archives of Internal Medicine, March 15, 1909.

CANCER.—In both rats and mice, carcinomatous and sarcomatous neoplasms have been caused to disappear by injections of adrenin, while they also prevented the growth of cancerous grafts. Reicher[85b] tried the same treatment in man. A sarcoma was reduced to one-third of its size, which third with the aid of X-rays and the high-frequency current was caused to disappear. Malignant lymphomata and a case of melanosarcoma were also favorably influenced. Injections of adrenalin around a tongue cancer also proved beneficial.[85c] [85d]

In personal inoperable cases adrenal gland seemed to prolong life by delaying the cachexia, especially when given with iron. Suggestive in this connection is that, in Reicher's words: "It is remarkable that during the treatments the patients increased much in weight—up to 14 pounds. There must be a constant anomaly of metabolism somewhere." I may recall in this connection that eight years earlier I had pointed out that the function of the adrenal secretion was to take up the oxygen of the air in the lungs and to sustain tissue oxidation, metabolism, and nutrition—thus accounting for the gain in weight Reicher noted. Ritchie[85e] recently reported the disappearance of a skin carcinoma under local applications of the 1:1000 solution of adrenin.

The desensitizing action of adrenalin by cataphoresis has been found by Reicher and Lenz[85f] to permit the use of nearly double the dose of X-rays.

[85a] Goldsieher: Wiener klin. Wochenschrift, June 2, 1910.

[85b] Reicher: Deut. med. Woch., Nu. 22, 1910, and Berliner klin. Woch., Nu. 20, 1911.

[85c] Echtermeyer: Berliner med. Woch., Aug. 21, 1911.

[85d] Holscher: Ann. des méd. de l'oreille, du larynx, etc., No. 7, 1912.

[85e] Ritchie: London Lancet, June 29, 1912.

[85f] Reicher and Lenz: Deut. med. Woch., Jan. 4, 1912.

Cardiac Disorders.—Kothe,[86] Rothschild,[87] Crile,[88] and others have obtained prompt recovery (after all other means had failed in Kothe's cases) in surgical heart-failure from intravenous injection of adrenalin in saline solution. Mankowsky,[89] Bates,[90] Floersheim,[91] Deeks,[92] and Boy-Teissier[93] have urged the value of adrenal preparations in cardiac disorders accompanied by weakness, particularly when there is dilatation, cyanosis, or œdema. Voight[93a] found 10 to 15 minims of adrenalin 1:1000 solution and 5-grain tablets of the gland valuable in cardiac dropsy and cardiac dyspnea.

In 1853 Brown-Séquard[94] found that the venous blood of the venæ cavæ contained some substance which contributed to the contractions of the heart. A contemporary promptly relegated this experimental fact to oblivion, by showing that carbonic acid, the only excitant credited to venous blood, failed to cause an exposed heart to contract. Had it not been for this misdirected experiment it is more than likely that Brown-Séquard, over fifty years before Oliver and Schäfer, would have discovered that, in Schäfer's words,[95] the adrenal extract produced "a powerful physiological action upon the muscular system in general, but especially upon the muscular walls of the blood-vessels, and the muscular wall of the heart." He would then, moreover, have reached the obvious conclusion to which I was subsequently led, that, inasmuch as the adrenal secretion passed by way of the adrenal veins to the inferior vena cava, it was inevitably carried to the right heart in the blood of this great channel, and that it was the adrenal secretion, therefore, which helped the heart to contract.

This explains the beneficial effects of adrenal preparations in adynamic heart disorders. Their active principle *via* the venæ cavæ excites *directly* the muscular elements of the right heart. Besides this, however, the entire cardiac muscle is also, from my viewpoint, excited *indirectly*. The adrenal active principle being carried by the venous blood from the heart to the pulmonary air-cells, it is added to that already in the blood, and becomes converted into the albuminous constituent of hæmoglobin, which, as we have seen, sustains oxidation. In this form it returns from the lungs to the left ventricle, with the arterial blood it has enriched, to be distributed to the body at large. When we recall that the first arteries given off by the aorta are the coronaries, whose branches supply the heart muscle proper, it becomes evident that the entire heart is the first to receive blood freshly laden with oxygen. On the whole, the adrenal secretion itself contributes to the heart's working power in two ways: (1) by enhancing directly the contractile power of its right ventricle, and (2) by sustaining oxidation and metabolism of the entire cardiac muscle.

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[86] Kothe: Centralbl. f. Chir., Aug. 17, 1907.
[87] Rothschild: Therapie der Gegenwart, June, 1908.
[88] Crile: Amer. Jour. Med. Sci., April, 1909.
[89] Mankowsky: Russian Arch. of path., Clin. Med. and Bact., March, 1898.
[90] Bates: Medical News, March 2, 1900.
[91] Floersheim: New York Medical Journal, Oct. 6, 1900, and May 4, 1901.
[92] Deeks: Montreal Medical Journal, Nov., 1901.
[93] Boy-Teissier: Arch. gén. de méd., Aug. 23, 1904.
[93a] Voight: British Med. Journal, March 9, 1912.
[94] Brown-Séquard: "Experimental Researches Applied to Physiology and Pathology," p. 104, 1853.
[95] Schäfer: *Loc. cit.*, vol. i, p. 951, 1898.

Emphasis must be laid upon an important practical fact in this connection, namely: that the obvious purpose of the direct aid the right ventricle receives from the adrenal secretion is to assist the walls of this ventricle in projecting the venous blood into the lungs. This explains the rapidity with which cardiac dyspnœa is relieved by adrenal preparations; they not only restore to the right ventricle its power to drive the venous blood adequately to the air-cells, but they supply it with the pabulum which enables it to absorb from the air enough oxygen to restore the general respiratory equilibrium. The increased metabolic activity in the vascular muscles being also enhanced, passive œdema is also caused to disappear, while the dilated heart tends to resume its normal dimensions.

Whether given orally, hypodermically, or intravenously, therefore, adrenal gland, through the agency of what active principle it happens to contain, enhances the contractile power of the heart. Mankowsky[86] found that its efficiency was best shown in cardiac weakness and threatening collapse, and all evidence available points in the same direction. Floersheim states that when powdered adrenal is placed on the tongue, mixed with saliva and masticated thoroughly, its effects appear within ten seconds. At other times it takes ten minutes to regulate a weak, irregular pulse, but the usual time has been between two and three minutes.

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[86] Mankowsky: Russian Archives of Pathology, March, 1898.

The dried gland in daily doses of 1½ to 3 grains (0.1 to 0.2 Gm.) is used in Europe. Whether our preparations are weaker or not I cannot tell, but the fact remains that such doses have not proven active in my practice, 2 grains (0.13 Gm.) three times daily, when a good preparation is available, being necessary to obtain appreciable effects, *i.e.*, such effects as can readily, and with more accuracy, be obtained with digitalis. Kothe[97] injects 20 drops (1.23 c.c.) of the 1:1000 solution of adrenalin in 1 quart of saline solution intravenously. John[98] injects slowly, in the same manner, 3 to 15 minims (0.18 to 0.92 c.c.) of adrenalin in 1½ drachms (5.55 c.c.) of saline solution. It has been used subcutaneously in 15 (0.92 c.c.) or more minims in ½ to 1 pint (250 to 500 Gm.) several times daily if necessary by Josué and others. Netter gives 10 to 20 drops (0.62 to 1.23 c.c.) or more by the mouth, but also subcutaneously in saline solution, when larger doses are required.

During the war, Peabody[98a] found adrenalin very helpful in the treatment of the irritable heart of soldiers. He injected 0.5 c.c. (8 minims) of the 1:1000 solution. He also observed an increase in the depth of respiration and a rise of blood-pressure.

The indications of adrenal preparations are, as stated, those in which weakness of the myocardium exists, though I would fear their use when degeneration is present, owing to the marked increase of vascular tension they cause, and the greater resistance thus imposed upon the heart. Their value is manifest where marked and threatening cardio-vascular adynamia exists, and in cardiac collapse in the course of infections, which is due, as I have shown under "terminal hypoadrenia," to arrest of adrenal functions. In such cases, especially where urgency prevails, adrenal medication promptly restores the arterial tension; the cardiac beats become more ample and regular, and the—perhaps suspended—pulse resumes its normal strength and rhythm.

In the treatment of valvular and other cardiac disorders, digitalis is more reliable, and it can be adjusted to the needs of each case with greater precision.

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[97] Kothe: Therapie der Gegenwart, p. 95, 1909.
[98] John: Münch. med. Woch., p. 1221, 1909.
[98a] Peabody: Jour. Amer. Med. Assoc., lxxi, p. 1912, 1918.

Respiratory Disorders.—We have seen that adrenal preparations enhance the vigor of the cardio-vascular contraction. The asthma often met with in elderly people is thus promptly relieved by these agents. This applies also to true asthma, as first shown by S. Solis-Cohen.[99] This result is explained, from my viewpoint, not only by the increased oxygen intake and the improved tissue oxidation just mentioned, but also by the more perfect hydrolysis of the toxic wastes to which the spasm of the bronchial muscles, and therefore the asthmatic paroxysms, are due. This introduces, however, an important feature of the problem, to wit, the participation of the whole organism in the improved oxygenation.

The prompt arrest of a paroxysm of asthma by the hypodermic injection of 5 to 10 drops (0.31 to 0.62 c.c.) of the 1:1000 solution of adrenalin chloride, first recommended by Kaplan, has been termed "inexplicable" and "marvelous"; but if the adrenal principle is considered as the active factor in general oxidation, and it is recalled that, according to Takamine, one two-hundred-thousandth of a grain (0.00000033 Gm.) of adrenalin (and this applies as well to other adrenal principles, such as suprarenalin, epinephrin, etc.) suffices to awaken physiological action, one can readily understand why many times this dose will produce therapeutic effects. Especially does this assert itself when we take into account a fact I have long urged, to wit, that we must look upon the active principle of the adrenal secretion not merely as a reducing agent, but as a *catalyzer* which, though remaining itself stable, can take up oxygen and transfer it with extreme rapidity, and in relatively enormous quantities, to the hæmoglobin, and from this compound to the tissue-cells. The adrenal active principle has not only been found in the red corpuscles by Mulon, as we have seen, but its catalytic action, first pointed out by Poehl, meets precisely the conditions deemed necessary by Moritz Traube, in 1858, to explain the massing of oxygen in the tissue-cells through its all-powerful catalytic action.

It has been noticed that a rise of blood-pressure does not always occur when it is low, when adrenalin is injected into the tissues, but this is due to its slow absorption, though the asthmatic paroxysm is aided at once. The rise of blood-pressure is hastened, according to Miles and Mulleberg, when the area in which the remedy was injected is massaged. Spraying the nose with a 1: 4000 or stronger solution of adrenalin or suppositories containing this agent has also been found capable of arresting paroxysms of asthma by Matthews. Aronsohn applies to the nostrils an ointment of vaselin and lanolin, of each, 1 drachm (4 grammes), containing 30 to 60 minims (1.85 to 3.7 c.c.) of 1: 1000 solution of adrenalin chloride. Weiss[99a] recommends an injection of adrenalin $^1/_{80}$ grain and pituitary extract $^2/_3$ grain in 15 minims of water. A second injection was required in only 10 out of 300 cases.

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[99] Solis-Cohen: Jour. Amer. Med. Assoc., May 12, 1900.

In hay fever the nasal spray referred to above was, at one time, used extensively, but it eventually proved more harmful than beneficial. By exhausting the contractile power of the nasal mucosa it caused the latter to relax and to block the respiratory area. If used at all, it should be only for a short time. Matthews[99b] uses a 1: 1000 solution in severe cases and 1: 2000 or 1: 4000 in milder ones. Far more efficient is the adrenalin ointment 1: 1000, to reduce the turgescence of the nasal mucosa, keeping the latter down by means of a 10-grain to the ounce of liquid petrolatum spray, between times.

Solomon Solis-Cohen recommends the use of adrenalin tablets, beginning with $^1/_{50}$-grain (0.00132 Gm.) doses, and increasing the latter, if need be, as the patient becomes accustomed to the use of the remedy until $^1/_{10}$ grain (0.0066 Gm.) is given. The tablets are allowed to dissolve on the tongue. If the patient can remain in a dark room to avoid the reflex excitation of the sensitive centers, the remedy is given less often.

Ascites and Other Effusions.—In this condition, there is a more or less great loss to the circulatory blood of its adrenal principle, owing to the accumulation in the peritoneal cavity of a more or less great volume of its serum. The latter being, as I have shown, the intermediary between the red corpuscles and the tissues for the transmission of the adrenoxidase to the latter, the ascitic fluid deprives the body of part of its oxidizing principle, *i.e.*, transfers a given proportion of it where it cannot carry on its normal functions. In some cases, in fact, as in one recently observed by Bean,[100] the serum may be bloody. The marked anæmia and asthenia which complicate these cases speak in favor of this view.

[99a] Weiss: Deutsche med. Woch., Sept. 19, 1912.
[99b] Matthews: British Med. Jour., Feb. 19, 1911.

That, in addition, the adrenal principle should prove useful in these cases, suggests itself, since they would restore to the organism that which is so essential to its physiological welfare. Fleischer and Loeb[101] found that injections of adrenalin not only improved the general condition, but also that they increased the rapidity of absorption of the fluid from the peritoneal cavity. Tyson and Jump[102] resorted to this measure in 3 cases. In the first patient ascites was due to chronic parenchymatous nephritis associated with moderate regurgitation at the mitral valve. Tapping had already been performed three times. Nine injections of adrenalin chloride were then given in the space of about two weeks, the original dose used being 7½ minims (0.5 c.c.) of a 1:1000 solution, rapidly increased to 30 minims (2 c.c.). The first 5 injections were given on successive days. After the third injection the line of dullness in the abdomen began to descend, and after the sixth ascites was barely demonstrable. The patient had two attacks of pulmonary œdema during the treatment, but stated that he had had previously several such attacks. The quantity of urine passed gradually rose during the treatment, the daily output at its termination being from 70 to 80 ounces (2100 to 2400 c.c.). Progressive improvement followed. As to the question whether the adrenalin had some influence upon the kidneys in addition to that on the absorptive power of the peritoneum, the fact that the patient had already been under treatment for a long time, which treatment had apparently been beneficial, leads to a conclusion in the negative.

The third patient was suffering from an abdominal carcinoma, probably arising in the stomach and extending to the omentum. The first injection of 30 minims (2 c.c.) apparently diminished the amount of fluid. The injections were gradually increased to 60 minims (4 c.c.), 12 in all being given, after which, no improvement being noted, paracentesis became necessary. The character of the causative disorder, however, could but defeat the curative value of the adrenal principle. In Bean's case, from which nearly sixty gallons of fluid, sanguinolent at times, we have seen, complete recovery occurred.

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[100] Bean: Chicago Medical Times, Sept., 1910.
[101] Fleischer and Loeb: Jour. Exper. Med., vol. xii, No. 3, 1910.
[102] Tyson and Jump: Therapeutic Gazette, Jan., 1911,

Satisfactory results have also been obtained in serous effusions in the pleura and tunica vaginalis after aspiration, by injecting into the cavity from 8 minims (0.5 c.c.) to 2 drachms (8 Gm.) of adrenalin in four times the quantity of saline solution.

General Indications of Adrenal Preparations.—The list of disorders in which adrenal preparations have been, and are being, employed could be greatly extended, but I have limited myself to those in which their use has proven advantageous in the hands of a sufficiently large number of practitioners to warrant their being added to our trusted remedial agencies. In a certain number of diseases they may even be said, interpreted from my viewpoint, to exceed other means at our disposal in value. These are:—

1. Addison's disease. In this affection adrenal preparations compensate for the deficiency of adrenal secretion, and, therefore, for deficient general oxidation, metabolism, and nutrition. The dosage should be adjusted to the needs of each case. Beginning with 3 grains (0.2 Gm.) of the desiccated extract three times daily after meals, the dose should be gradually increased until the temperature and the blood-pressure become normal, when the last dose should be maintained. (See page 103.)

2. Surgical heart-failure; collapse from hæmorrhage, shock, asphyxia, and submersion. Here the adrenal active principle (suprarenalin, adrenalin, etc.), as a catalyzer and a constituent of the hæmoglobin, promotes energetically the intake of oxygen and its utilization by the tissue-cells, including the muscular elements of the cardiovascular system, and thus causes them to resume their vital activity.

3. The toxæmias, including bacterial infections, surgical septicæmias, etc., when collapse threatens, especially when a persistently low blood-pressure, hypothermia, and cyanosis are present. Besides enhancing pulmonary and tissue respiration, the adrenal principle, administered in the same way, enhances the efficiency of the immunizing process. (See pages 113 and 124.)

4. Capillary hæmorrhage from the pharyngeal, œsophageal, gastric, or intestinal mucous membrane. The mastication of tablets of adrenal substance, or the oral use of powdered adrenal substance in 5-grain capsules, arrests the flow by causing active metabolism in the muscular elements of the arterioles of the mucosa and constriction of these vessels.

5. Asthenic cardiac disorders with dilatation of the right ventricle, dyspnœa, and possibly cyanosis and œdema, owing to the direct action of the adrenal principle on the right ventricle and improved oxidation and metabolism in the cardiovascular muscles and the tissues at large. Tablets of from ½ to 2 grains (0.033 to 0.13 Gm.) of the desiccated gland can be taken after meals.

6. Asthma, to arrest the paroxysms, by augmenting the pulmonary and tissue intake of oxygen and the cardio-vascular propulsion of arterial blood. From 5 to 10 minims (0.31 to 0.62 c.c.) of the 1: 1000 solution of suprarenalin or adrenalin in 1 drachm of saline solution should be injected, drop by drop, into a superficial vein, or hypodermically.

7. To prevent the recurrence of serous effusions in the pleura, the peritoneum, the tunica vaginalis, etc., after aspiration, by reducing the permeability of the local capillaries and restoring the circulatory equilibrium.

8. In neuralgia or neuritis, as pointed out by Carleton, applied to the cutaneous surface over the diseased area to produce ischæmia of the hyperæmic nerves and thus arrest the pain. One to 2 minims (0.12 c.c.) of a 1 to 1000 adrenalin ointment should be applied by inunction.

PITUITARY ORGANOTHERAPY.

I have submitted elsewhere in this work the many reasons which have led me to differ from those who consider the pituitary body as a secreting gland, and to attribute to this organ the functions of a composite nerve-center. Pituitary organotherapy, though of marked value, does not mean to me, therefore, as did the organic preparations reviewed so far in the present chapter, the scientific use of a substance which carries on well-defined functions in the body, but rather the use of a tissue rich mainly in *chromaffin substance* and nucleins, or at least in substances capable of producing jointly the effects of adrenal preparations (a generally recognized fact) modified, and indeed improved, through their combination with other components of the pituitary body. I may recall in this connection that of the two lobes, as shown by Howell, Silvestrini, Thaon,[103] and others, the posterior is the only one whose extracts are active therapeutically, but that, as shown by Crowe, Cushing, and Homans,[104] it is not removal of this lobe which causes death in animals—as it should, were it like the adrenals and the thyroparathyroid body, a secreting gland important to life—but removal of the anterior, which therapeutically is inert.

What explanation of the rôle of pituitary preparations I will offer, therefore, will not take the so-called secretion into account; it will utilize the only certain fact we have at our disposal for this purpose, viz., that, as shown by Wiesel, the posterior lobe is rich in chromaffin substance—the active component of adrenal tissue—and that it is mainly the physiological effects of this substance—though advantageously modified as a therapeutic agent through its combination with other constituents of the same tissue, I repeat—that we witness.

The phenomena awakened by pituitary are strikingly those of adrenal preparations. Mairet and Bosc[105] found, in 1896, that subcutaneous injections of pituitary extract produced a rise of temperature which lasted but a couple of hours. An intravenous dose produced marked myosis, slowing of the respiration, powerful cardiac beats, and hyperthermia as main signs, the animals recovering, however. Schäfer and Vincent[106] then found that pituitary substance raised the blood-pressure—besides containing a depressor substance—and that this substance when applied to mucous membranes caused blanching, as is the case when a solution of adrenalin is applied. They also noted that in small mammals it caused, in toxic doses, paralytic symptoms which they also consider analogous to those caused by adrenal extracts. According to Jas. Barr,[107] pituitary extract actively produces arteriosclerosis, and it is also known to produce glycosuria. In other words, it awakens all the typical phenomena, physiological and pathological, to which the adrenal product gives rise.

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[103] Thaon: L'hypophyse, p. 99, 1907.

[104] Crowe, Cushing, and Homans: Bulletin of the Johns Hopkins Hospital, May, 1910.

[105] Mairet and Bosc: Arch. de physiol., p. 600, 1896.

[106] Schäfer and Swale Vincent: Jour. of Physiol., p. 87, vol. xxv, 1899.

[107] Barr: Lancet, Nov. 13, 1899.

The marked advantage of pituitary—owing, doubtless, to the fact that it is bound up in organic combination with other components of the organ—is that it sustains the rise of blood-pressure and is reliable in shock and other emergency cases. It seems also to sustain the temperature and the muscular tone, cardiac, vascular, intestinal, and uterine, longer than the adrenal active principle. It possesses also a great practical advantage over adrenalin and other adrenal principles in that it can be administered by the mouth without compromising its effects. Moreover, pituitary preparations have seemed to me clinically to produce the pharmacodynamic effects of both the cortex and of the medulla of the adrenals.

The pituitary is now granted *four* internal secretions: one each to the anterior and posterior lobe, one to the infundibulum, and one to the organ as a whole. All of these are more or less used in practice, particularly the *anterior lobe,* in 3 to 5 grain (0.2 to 0.33 Gm.) doses, *t.i.d.,* in deficient growth and adipositas, infantilism, mental backwardness, deficient sexual development and asthma; the *whole gland* in 3 to 5 grains (0.2 to 0.33 Gm.), *t.i.d.,* in all of the foregoing disorders, and general asthenia, neuralgia, tachycardia, due to low blood tension and other cardiac conditions referred to below, and particularly the *posterior lobe,* now recognized by the U. S. P. (1916) as the *hypophysis sicca,* the dose of which is ½ grain (0.033 Gm.), used mainly in the disorders described below. Another official preparation is the *liquor hypophysis,* a liquid preparation of the posterior lobe, the dose of which is 5 to 15 minims (0.3 to 1 c.c.), used mainly in obstetrics and surgery, as we shall see.

A new product, tethelin, has been isolated by T. B. Robertson,[108] but it is not as yet available on the market.

CARDIAC DISORDERS.—As shown by Rénon and Delille,[108a] pituitary gland raises the depressed arterial tension and corrects purely functional disorders of rhythm.

It is recommended in doses ranging from 3 to 6 grains (0.2

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[108] Robertson: Endocrinology, Jan., 1917.

[108a] Rénon and Delille: Soc. de Thérap., Jan. 22 and April 23, 1907, and Congrès de Médecine de Paris, Oct., 1907.

to 0.4 Gm.) of the whole gland, in myocardial weakness, particularly in that due to infections when the blood-pressure is receding, the pulse is becoming more rapid, and the urine scanty. While less active than digitalis as a diuretic, it nevertheless serves a valuable purpose in this connection. It is advantageous in mitral disorders when there is hyposystole and in chronic myocarditis, particularly that due to alcoholism. It is also useful in the tachycardia of certain neuroses and during menopause. These results have been confirmed by Trerotoli,[109] Parisot,[110] and others.

It is contraindicated in aortic affections in any disorder in which high vascular tension prevails, and where there is a tendency to anginal pains, which it tends greatly to aggravate.

Pituitary gland is preferred to adrenal and particularly adrenalin, as stated above, when the action is to be sustained, the former being useful in urgent cases. Rénon and Delille, however, prefer digitalis, and recommend pituitary gland only when the latter fails. Leonard Williams,[111] on the other hand, deems it superior to digitalis, strophanthus, strychnine, and other classic tonics in what he terms the "runaway heart of toxic states," influenza, pneumonia, bronchitis, etc., with tachycardia, but low blood-pressure, and in all cases in which there is posttoxic cardiac debility. In these cases—which, from my viewpoint, are instances of pure hypoadrenia—Williams regards pituitary preparations superior to any remedy at our command.

In heart-failure and shock, it has been highly recommended by Mummery and Lymes and Bell and Wray, 15 minims (0.92 c.c.) of the extract being injected intramuscularly.

R. A. Bate,[111a] after using the liquor hypophysis in over 100 cases of cardiovascular, and metabolic atony and deficient defensive activity regards pituitary as the most effective therapeutic agent at our disposal in endocrine therapy.

OBSTETRICS.—Dale[112] found experimentally that extract of pituitary caused "direct stimulation of involuntary muscle without any relation to innervation." Fröhlich and Frankl-Hochwart[113] then ascertained that it caused contractions of the pregnant uterus in rabbits, while Foges and Hofstetter[114] resorted to this property to check post-partum and other uterine hæmorrhages in 63 cases. The extract proved worthless by the mouth; but when injected intramuscularly, marked uterine contraction appeared within five minutes and lasted a long while in most cases. Voigts[114a] found pituitrin most satisfactory in 60 cases; 1 c.c. (15 minims) sufficed. Pouillot and Vayssières[114b] give 7½ minims intramuscularly several times daily in all adynamic or hemorrhagic conditions. Trapl[114c] recommends it in placenta previa of the marginal type. A number of authors have recommended it for menorrhagia and metrorrhagia. Pituitary is useful, in fact, in all forms of hemorrhage of the genital system.

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[109] Trerotoli: Rivista critica di clinica med., Nos. 22 and 23, 1907.
[110] Parisot: Pression arterielle et glandes à sécretion interne, Paris, 1908.
[111] Williams: Clinical Journal, May 18, 1910.
[111a] Bate: Louisville Mthly. Jour. of Med. and Surg., Sept., 1915.
[112] Dale: Biochemical Journal, 1909.
[113] Fröhlich and Frankl-Hochwart: Wiener klin. Woch., No. 27, 1909.

Norris[114d] never uses pituitary extract without exhausting his abilities in obstetric diagnosis. He considers that healthy multiparas with relaxed birth canals offer the widest and safest fields. For inertia in the early stage of labor, the sleep of morphine, chloral, or scopolamine is preferred; in the advanced stages of labor, pituitary extract, he says, often will wisely keep forceps innocuous. The uterus, after the tumultuous visitation of pituitary extract, usually needs the steadying hand of ergot. Half doses are more often to be employed than full doses.

A large number of observers have, however, brought out some dangerous features. Nagy[115] observed that it decreased the action of the fetal heart. Spaeth[115a] had 2 cases of death in the newborn which are ascribable to this cause. Various authors have noted tetanoid spasm of the uterus. J. Clifton Edgar[115b] states that both small and large doses have caused, through this defect, fatal compression of the fetus, premature separation of the placenta, and deep rupture of the cervix, his experience being based on 70 cases. In 39 of these in the first and second stages there were 2 and probably 4 still-births, and 3 instances of deep laceration requiring sutures to control the bleeding.

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[114] Foges and Hofstetter: Zeitschr. für Gynäk., No. 12, 1910.
[114a] Voigts: Deut. med. Woch., Dec. 7, 1911.
[114b] Pouillot and Vayssières: Presse médicale, No. 4, 1913.
[114c] Trapl: Monats. chr. f. Geburtsh. u. Gynäk., Oct., 1912.
[114d] Norris: Amer. Jour. of Obstetrics, May, 1915.
[115] Nagy: Zentralbl. für Gynecol., March 9, 1912.
[115a] Spaeth: *Ibid.*, Feb. 1, 1912.
[115b] Edgar: New York Med. Jour., p. 150, July 19, 1912.

Several instances of rupture of the uterus under the use of pituitrin have also been reported. DeLee[115c] no longer uses it.

Ott and Scott[116] found infundibulin, *i.e.*, extract of the posterior lobe, to act as a powerful galactagogue in the goat. So far, however, it has not been tried in women.

INFECTIOUS DISEASES.—In this general class of disorders the use of pituitary acts, from my viewpoint, and in keeping with the effects of adrenal preparations, by enhancing the immunizing activity of the blood and the tone of the cardio-vascular system when it is depressed.

Rénon and Delille[117] found that in typhoid fever it raised the blood-pressure, slowed the pulse, increased diuresis, and improved the patients in general, hastening convalescence noticeably. In diphtheria, in which the toxin reduces the vascular tension and promotes cardiac complications, it lowered the pulse-rate, raised the blood-pressure, and increased diuresis. In erysipelas it seemed to hasten the favorable evolution of the disease. In pneumonia it raised the blood-pressure when this became low, but without influencing favorably the evolution of the disease. In bronchopneumonia, however, the opposite proved to be the case, considerable benefit being noted. Influenza was found to be very favorably influenced, rapid recovery resulting in patients aged, respectively, 80 and 63 years. This was confirmed by Azam,[118] in the infectious form. Rénon and Azam enumerate the phenomena which, in infectious diseases, indicate the need of pituitary: 1, a fall of the arterial tension; 2, quickening of the pulse and, as complementary minor phenomena, insomnia, anorexia, abnormal sweating, and heat flushes. Under the influence of pituitary there occur: 1, increase of arterial tension; 2, slowing of the pulse, with increase of power and amplitude; 3, increased diuresis; 4, increase in weight; 5, hastening of convalescence.

In several cases of tuberculosis treated by Rénon and Delille, the results were not, on the whole, encouraging. In a case of Addison's disease complicating tuberculosis, however, there was a notable rise of the blood-pressure and diminution of the asthenia. Trerotoli had already noted the beneficial effects of pituitary body in Addison's disease—a fact which further suggests that the active agent of pituitary substance is its adrenal component.

[115c] De Lee: Trans. A. M. A.; Med. Rec., June 22, 1912.

[116] Ott and Scott: Monthly Cyclopædia and Medical Bulletin, Nov., 1910.

[117] Rénon and Delille: Bull. gén. de Thérap., Feb. 8, 1907, and Delille: *Loc. cit.*

[118] Azam: Jour. de méd. et de chir. pratiques; Practitioner, March, 1908.

ACROMEGALY.—The possible value of pituitary extracts in acromegaly, a disease of the pituitary body, has naturally suggested itself, but, although a few of the symptoms, the headache, lethargy, and amnesia, were relieved in some, no cures were obtained. This subject has already been referred to on page 607.

Analysis of the cases reported as benefited suggests an explanation of its mode of action, however, one quite apart from any functional relationship with the organ as the source of an internal secretion, but entirely in keeping with the presence in the pituitary preparation of adrenal secretion in organic combination. Marinesco[119] observed that it was the extremely violent headaches that were relieved, there being no benefit otherwise excepting perhaps increased diuresis. Kuh,[120] obtaining no favorable result, withdrew the remedy, but the patient begged to be given the powders again, having found his headache much more intense when he failed to take them. The same observation had been recorded by Cyon,[121] the patient, an obese child of 12 years, having besides lost twenty pounds in weight. What benefit was obtained in 1 case out of 7 cases treated by Kinnicutt[122] was also limited to the headache and neuralgia. Leszynsky,[123] after a prolonged trial in 2 cases, wrote: "While some published reports as to the efficacy of the preparations of the sheep's gland have seemed quite encouraging in so far as the relief of headache and of paræsthesia of the hands is concerned, it is the general consensus of opinion that it in no way influences the progress of this disease."

Still, the relief of the headache and paræsthesiæ indicates some potent action. This is accounted for if the adrenal principle is considered as the active agent of pituitary preparations, since, as Langley has shown, it is principally upon the

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[119] Marinesco: Semaine Médicale, Nov. 13, 1895.
[120] Kuh: Jour. Amer. Med. Assoc., Feb. 1, 1902.
[121] Cyon: Progrès Medical, Nov. 26, 1898.
[122] Kinnicutt: London Lancet, vol. ii, p. 172, 1896.
[123] Leszynsky: Medical Record, June 30, 1900.

arterioles that the adrenal principle acts, a view which has now become classic. Such being the case, the tumor of the pituitary, or the compressed tissues around it, receive less blood through their constricted arterioles, and the sensory terminals of the peripheral likewise. The resulting ischæmia of these tissues thus accounts for the diminution of pain—as long only as the remedy is administered.

EXOPHTHALMIC GOITER.—Rénon and Delille[124] obtained considerable improvement in this disease by the use of pituitary gland. From the fourth to the fifth day, the sleeplessness, tremor, digestive disturbance, sweating, and sensation of heat were considerably lessened. The tachycardia improved less rapidly, the pulse becoming slower gradually and attaining its slowest rate toward the fifteenth day. The arterial tension also rises steadily, attaining the maximum toward the third week, falling again somewhat, but not to the former low level. Some diminution of the exophthalmus occurred, but the goiter was not reduced. The dose administered was 4½ grains (0.30 Gm.) of the whole pituitary (ox) gland daily, a dose which they deem advisable to increase to 7½ grains (0.50 Gm.) in divided doses daily. The symptoms tend to return, however, on discontinuing the remedy. Cases subsequently treated were also benefited, but no cures were effected.

This mode of action, from my viewpoint, corresponds precisely with that referred to under the preceding heading. We have seen in the fifth chapter that the main pathological condition, that to which all the prominent symptoms of exophthalmic goiter were due, was a general dilatation of the arterioles. Pituitary extracts causing constriction of these vessels as long as it is administered, it offsets for the time the morbid phenomena enumerated. That such is actually the case was demonstrated by Hallion and Carrion,[125] who found, experimentally, that pituitary extracts "always produced their effects by raising the arterial tension," producing at the same time "an intense vasoconstrictor action upon the thyroid body." Briefly, we have here precisely the physiological action necessary, the vasoconstrictor power of the adrenal component of the pituitary gland superseding the vasodilator action of the thyroid, the underlying cause of the disease.

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[124] Rénon and Delille: Soc. Oesthérap., March 13, 1907.
[125] Hallion and Carrion: *Ibid.*

NERVOUS AND MENTAL DISEASES AND MYOPATHIES.—Rénon and Delille used pituitary in 10 neurasthenics in whom tachycardia, irregular vascular tension, often below normal, a sensation of oppression, myasthenia, insomnia, and anorexia were present. In these cases, 3 to 5 grains (0.2 to 0.3 Gm.) daily proved remarkably useful, though no complete recovery was noted.

Delille and Vincent[126] obtained a complete recovery in a grave case of bulbo-spinal myasthenia by the simultaneous use of pituitary and ovarian extracts. Parhon and Urechia and Léopold-Lévi and de Rothschild[127] had also obtained favorable results with pituitary in similar cases. Browning[128] observed good effects in cases of chorea in which this disorder occurred in conjunction with stunted growth, as shown under the next heading.

In epilepsy, it was tried by Mairet and Bosc,[129] but only served to increase the number of attacks—a result to be expected, since Spitzka has shown that these were due to abnormal elevation of the blood-pressure. In some instances it provoked delirium.

Sollier and Chartier[130] tried pituitary in mental disorders and found it useful in depressive states. It raised the blood-pressure, reduced the pulse, suppressed profuse sweating, and improved the asthenia. The synthesis of perceptions and the association of ideas were improved, and mental operations were incited more promptly.

STUNTED GROWTH AND IMBECILITY.—In the case of a child of 3 years, which had shown the evidences of hypothyroidia with idiocy sufficiently to suggest the use of thyroid, Léopold-Lévi and de Rothschild found this agent useless. The case being attended with marked myasthenia, they administered pituitary extract 1½ grains (0.1 Gm.) twice daily, which corresponded with 7½ grains (0.5 Gm.) of the fresh gland. Marked signs of improvement appeared within a few days. The intelligence developed to a remarkable degree, and soon reached that of a child of a corresponding age, 3 years, though before the treatment it did not exceed that of a 7 or 8 months' infant. Two similar cases, one of which showed symptoms of Little's disease, were similarly benefited.

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[126] Delille and Vincent: Soc. de Neurol., Feb. 7, 1907.
[127] Léopold-Lévi and de Rothschild: *Ibid.*
[128] Browning: New York State Journal of Medicine, Sept., 1909.
[129] Mairet and Bosc: Arch. de Physiol., p. 600, 1896.
[130] Sollier and Chartier: Congrès de Dijou, Aug., 1908.

Browning[131] used pituitary only in undersized or backward children and youths with marked success. The reader is referred to the fifth and sixth chapters, in which these disorders are treated in full.

INTESTINAL PARESIS.—Bell and Hicks[132] have found pituitary extract of value in paralytic gaseous distention of the intestines. It never failed either in post-operative or other paresis if given intramuscularly, when the intestine begins to distend, in 15-minim (0.92 c.c.) doses, repeated in an hour, if required. The effect is then sustained by daily doses if need be. Kirmisson[133] obtained good results where intestinal paresis following operations for acute appendicitis, a stool sometimes following in 15 minutes. Davis and Owens[133a] also found that, used after the operation, it prevented postoperative nausea and vomiting.

According to E. H. King[134] by-effects of pituitary extract are: rise of blood-pressure, dyspnea, air hunger, and pallor; but these are transitory, and are negligible when contrasted with the lasting benefit secured in the majority of instances. Vomiting may be expected, and be welcomed, if the stomach contains intestinal contents; for in intestinal paresis the upper, rather than the lower, alimentary tract functions inadequately as the vent. Pituitary extract is injected, under aseptic precautions, into a vein—usually one near the elbow, though in fat persons a vein on the back of the hand is more available. In a given case of intestinal paresis, it affords an additional means of emptying the bowel, which is peculiarly applicable and transcends in efficiency any previously known. In uncomplicated post-operative cases its action is promptly curative, and it is possibly curative of functional, actual obstruction. Pituitary extract should be given very carefully when the heart rate is unusually high, 140 or more, when there is marked intermittence on the heart, or in cardiac decompensation. In angina pectoris, on account of the vasoconstriction produced by it, this agent is probably absolutely contraindicated.

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[131] Browning: *Loc. cit.*
[132] Bell and Hicks: British Medical Journal, March 27, 1909.
[133] Kirmisson: Bull. de l'Acad. de Méd., Jan. 29, 1918.
[133a] Davis and Owens: New Orleans Med. and Surg. Jour., lxx, p. 712, 1918.
[134] King: Med. Record, June 30, 1914.

ARTHRITIS.—B. H. Whitbeck[135] describes 13 cases of rheumatic arthritis treated by the daily intramuscular injection of a 1 per cent. solution of pituitary extract; only 2 failed to improve. Relief of pain, joint-fluid absorption, and increased activity were noted rather early in the treatment. General improvement and equalization of the pulse- and blood- pressure were also noticeable.

M. S. Macy[136] obtained good results in 3 consecutive cases of gonorrheal arthritis. All 3 had been under autogenous vaccines, as well as local antiseptic treatment for the infection of the genitourinary tract; but the arthritis, of some months' standing, had been very slightly, if at all, benefited. The treatment consisted in ionizing into the affected joints, by the high-frequency spark, of pituitary gland substance (in the form of tablets) triturated to a powder. Usually, 1 grain of the powder was employed at each treatment, but in one of the patients this was increased to 2 grains.

RACHITIS.—R. Klotz[137] tried pituitary with calcium carbonate in 5 infants, from 1 to 2 years of age, some of whom had received no benefit from the usual remedies. Although all 5 cases were severe, in two weeks all were able, for the first time, to stand upright and walk. Previously wasted from diarrhea, the children increased in weight and strength.

ASTHMA.—We have seen that adrenalin is used with benefit in the treatment of asthmatic paroxysms; unfortunately the arrest of suffering is ephemeral. Pituitary gland has been found equally effective and more lasting in its effects. Moreover, it may be administered orally and the paroxysms thus prevented. Suggestive in this connection, in so far as my own view that the effects are mainly due to the adrenal extractives it contains, is the observation of Reiss[138] that the first injection in his cases gave all the by-effects of adrenalin. Crookshank[139] treated 20 cases of bronchial asthma, giving 2-grain tablets of pituitary substance. The attacks became comparatively mild. In 2 of the cases the use of antispasmodics—stramonium, etc.—were rendered unnecessary. F. C. Warfel[140] also obtained "very marked improvement in the distressing train of symptoms in forty-eight hours," by means of 2½-grain tablets of the anterior lobe.

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[135] Whitbeck: Am. Jour. of Orthopedic Surg., Jan., 1915.
[136] Macy: Med. Record, June 19, 1915.
[137] Klotz: Münch. med. Woch., May 21, 1912.
[138] Reiss: Berliner klin. Wochenschr., July 19, 1915.
[139] Crookshank: London Lancet, March 14, 1914.

HEMOPTYSIS.—This distressing condition, so often rebellious to classic methods, was found amenable to treatment by means of extract of the posterior lobe by Rist[141] when injected intravenously. The results in 20 cases, ranging from the stage of consolidation to that of cavities, and including 1 case of pulmonary cancer and of pulmonary infarct, were instantaneous as to arrest of the hemorrhage, excepting in 1 case in which the patient failed to subject himself to rest and quiet. Recurrence having occurred in several instances, the second injection proved as efficient as the first. In only one instance did a third injection become necessary. Konikow[142] refers to a case, in which he injected 15 minims of pituitary liquid hypodermically, as "magical." Recurrence was also followed by arrest of the flow by the same measure.

OVARIAN ORGANOTHERAPY.

The fact that destruction or absence of the ovaries caused girls to grow without the general physical attributes of the female sex led Brown-Séquard to consider these organs as the source of an internal secretion. This view has been upheld by many observers who found that ovaries transplanted in the abdominal cavity, *i.e.*, elsewhere than in their normal location, restored to the other genital organs the power to develop and carry on their physiological functions.

Summarizing the labors of Fraenkel, Loeb and Novak, E. T. Hermann[142a] concludes that the ovarian corpus luteum supplies a sensitizing substance to the uterine mucosa which enables it to form the placenta. It aids fixation of the embryo, is essential for its development, initiates menstruation and activates development of the mammary gland and lactation. Its presence or absence determines menstrual activity.

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[140] Warfel: Indianapolis Med. Jour., July, 1915.
[141] Rist: Echo Médical du Nord, No. 903, 1914.
[142] Konikow: Boston Med. and Surg. Jour., Sept. 30, 1915.
[142a] Hermann: Minn. Med. Jour., May, 1918.

The *preparation* in general use is the desiccated gland, which may be given in doses of 5 to 10 grains (0.33 to 0.66 Gm.) twice daily. The fresh organ may be employed in 10- to 15- grain (0.6 to 1 Gm.) doses where the pharmaceutical product is not available. It soon loses its effect; small doses should first be given, then gradually increased.

Ovarian preparations have been tried in many disorders, but it is mainly in connection with those of the genital apparatus that they have been found of actual value.

Natural and Artificial Menopause.—In disorders occurring in the course of the physiological menopause, or when the latter is produced by bilateral oöphorectomy, ovarian preparations have proven of considerable value in a large proportion of cases since Brown-Séquard first introduced their use. Experience has shown, however, that the improvement lasts only as long as the agent is administered, and that, furthermore, certain phenomena—the palpitation, trembling, and "nervousness"—disappear earlier than the others, *i.e.*, the asthenia, flushes, irritability, and psychoses, though effects in all symptoms, including the cutaneous disorders,—especially acne rosacea and eczema,—are promptly realized, sometimes as early as the fourth day.

These effects are normally explained by the influence of the remedy on general oxidation and the improvement of the antitoxic functions of the blood, the imperfect hydrolysis of tissue wastes being the underlying cause of the phenomena other than the general asthenia.

The best results are obtained in young women who have grown obese after removal of the ovaries, or in whom obesity is due to ovarian insufficiency. In physiological menopause they are less marked, as a rule, and sometimes fail altogether to appear. In such instances, good results may sometimes be obtained by giving simultaneously 1 grain (0.066 Gm.) desiccated thyroid, or by depending upon the latter remedy alone. In congenital ovarian insufficiency, desiccated ovary has caused the appearance of menstruation.

Of late, however, the general attention has been centered upon the therapeutic use of corpus luteum, which often affords benefit where ovary alone fails.

The mode of action of ovarian preparations is suggested by the personal view submitted on page 479, concerning the general effects of the ovaries attributed to an internal secretion. This is that we are not dealing with a true secretion, but with the products of the adrenal rests in the organ, and particularly the corpora lutea. The chemical properties, tests, physiological effects, etc., were shown to correspond precisely; the cellular elements also showed the characteristic features of the adrenal cortex, that the kinship had been noted by Mulon and others.

An important fact which should not be overlooked, however, is that the active agent occurs in organic combination with other bodies. Hence the fact that, although investigations having for their purpose to isolate the active constituent of the corpus luteum have been numerous, they proved successful only in a relative degree. Iscovesco,[143] of Paris, has extracted from the corpus luteum as well as the entire ovary a number of lipoid substances, one of which, a yellowish, waxlike body, soluble in oil, was found to exert a pronounced stimulating action upon the genital system, injections into young female rabbits causing a striking enlargement of the ovaries and uterus to several times the size noted in control animals. He believes the lipoids isolated by him to represent the active internal secretion of the ovary, and produces evidence to the effect that the most active of the lipoids exists both in the corpus luteum and in the remaining tissue of the ovary. Some investigators, on the other hand, cling to the older view that the active ovarian principle is a protein substance occurring in conjunction with a lipoid or lipoids. Herrmann,[144] in a recent research, obtained from the corpus luteum, as well as from the placenta, a thick yellow oil, which turns brown upon oxidation in the air and powerfully excites the growth of the reproductive organs. In common with Frank and Rosenbloom,[145] he believes that the active substance is not a lipoid, but is simply carried along with the lipoids when these are extracted from the luteal tissue as a whole. No preparation of an active principle of the corpus luteum is as yet available for therapeutic use, unless the lipoid preparations of Iscovesco, already used by him with satisfactory results in clinical work, are to be considered such.

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[143] Iscovesco: Revue de Gynécol. et de Chir. Abdom., vol. xxii, p. 161, 1914.
[144] Herrmann: Monatshefte f. Geburts. u. Gynek., Jan., 1915.
[145] Frank and Rosenbloom: Surgery, Gynec. and Obst., Nov., 1915.

CORPUS LUTEUM ORGANOTHERAPY.

Menstrual Disorders; Menopause; Oöphorectomy.—Corpus luteum therapy has been applied chiefly in disturbances of menstruation and for the removal of the symptoms of the menopause, physiological or artificial, such as hot flashes, spells of psychoneurotic manifestations, digestive difficulties, vesical irritation, etc. The best results have been obtained in the climacteric group of cases. Marked, though not always complete, relief is usually experienced by these patients, the use of the remedy for an indefinite period being, however, necessary if permanency of result is to be secured. Dannreuther[146] has reported 2 cases of pruritus vulvæ associated with the menopause in which the itching was relieved with striking promptness by corpus luteum. He urges routine administration of the drug in all cases approaching the menopause as well as after hysterectomy and oöphorectomy, whether partial or complete. In some cases where but one ovary has been removed, compensatory activity by the other proves insufficient; corpus luteum therapy under these conditions is likely to prove beneficial.

Menstrual disturbances amenable to corpus luteum include, in particular, functional amenorrhea and dysmenorrhea of ovarian origin. Among patients with the former condition Dannreuther lays stress on the slightly obese, anemic, pale type of young woman who begins, soon after puberty, to complain of headache, malaise, nervousness, and constipation, together with scanty menstruation and, possibly, acne vulgaris. In such patients, by combining corpus luteum with hygienic treatment and tonic remedies, marked general improvement as well as stimulation of the menstrual flow can often be secured. Leighton[147] reports excellent results from the use of corpus luteum in a certain proportion of cases of dysmenorrhea, in particular those showing symptoms of ovarian insufficiency, such as irritability, malaise depression, headache, and scanty menstruation, with pain, especially on the first day of the period. This observer has become convinced that there occur cases of dysmenorrhea of which the chief cause is deficient action of the natural corpus luteum; the striking effect of the remedy in these patients would thus easily be accounted for.

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[146] Dannreuther: Jour. Am. Med. Assoc., Jan. 3, 1914.

[147] Leighton: Amer. Jour. of Obstet., Nov., 1915.

Sterility; Infantile Generative Organs; Habitual Abortion; Hyperemesis of Pregnancy.—Additional conditions in which corpus luteum has proved beneficial, though less consistently than in the disorders already referred to, are sterility, infantilism of the reproductive organs, repeated abortions, and hyperemesis in the early months of pregnancy. Sterility is, of course, influenced only in the absence of gonococcal or other infection as well as of cervical stenosis. Elliott[148] has reported the case of a married woman of 27 years, masculine of figure, with uterus of walnut size and ovaries impalpable, menstrual show only three or four times during life, epistaxis, and sexual feeling almost absent, in which corpus luteum therapy, coupled with uterine massage, was followed by a partial return of menstruation and by pregnancy. Dannreuther found the drug of similar value in 2 cases of repeated abortion of obscure origin. In the hyperemesis of pregnancy corpus luteum has been employed by a number of observers with variable, but often distinctly favorable results. J. C. Hirst[149] obtained excellent results in 4 out of 5 cases and deems it superior to any other for the treatment of nausea in pregnancy.

The two most important prerequisites to success in the use of this drug appear to be (1) the selection of a preparation made exclusively from the corpora lutea of pregnant animals and (2) due attention to the fact that the action of the drug is frequently slow in asserting itself, and that the drug should be given up only when thorough trial has demonstrated its lack of efficiency.

The material now chiefly employed consists of the dried corpora lutea of cows or sows, exhibited in tablets, capsules, or cachets in doses of 5 to 10 grains three times a day. The dried substance represents usually about five to six times its weight of fresh luteal tissue. Preparations made exclusively with the corpora lutea of pregnant animals are considered the most efficient. A preparation termed "luetin," now on the market, is administered in 20-grain doses three times a day.

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[148] Elliott: Jour. Am. Med. Assoc., April 4, 1914.

[149] Hirst: Jour. Am. Med. Assoc., Feb. 26, 1916.

ORCHITIC OR TESTICULAR ORGANOTHERAPY.

From the standpoint of therapeutics, testicular preparations can hardly be regarded as of more than historical interest. The influence of the testicles on the body at large is well known. Castration influences the development of the organism in many particulars. Eunuchs preserve to a certain extent the characteristics of infantilism, the skin remaining soft and white, their muscles flabby and weak, and the voice high pitched. Yet they are usually tall, owing to inordinate growth of the bones. They lack courage, initiative, and intelligence. This suggests, therefore, that the testicles do not carry on genital functions only. Brown-Séquard taught that they carried on a dual rôle: 1st, procreation; 2d, the production of an internal secretion which stimulates and sustains the energy of the nerve-centers and cord, and capable, moreover, of endowing the individual with physical, moral, and intellectual characteristics of sex. His own physical and intellectual activity having been greatly improved at the age of 72 years, by injections of an extract prepared from the testes of young dogs, he concluded that it possessed marked therapeutic value. No one who, as I did, saw Brown-Séquard before and after he had submitted himself to this treatment could stretch his imagination sufficiently to attribute the change in his appearance to auto-suggestion. He literally looked twenty years younger.

The prevailing opinion is that the beneficial effects obtained from testicular preparations are not due necessarily to an internal secretion, though the existence of such is not denied, but to nucleo-albumins, substances that are rich in phosphorus, resembling greatly lecithins and glycerophosphates. From my viewpoint (see page 473), they are mainly due to extracts of the adrenal rests they contain, in organic combination with nucleins.

Dixon states that a constituent of orchitic extract is unaltered by boiling; McCarthy holds that it increases the force and regularity of the heart muscle as does digitalis. It enhances the resistance to disease, increases the production of urea, and also acts directly upon the cardio-vascular system. Moreover, as shown by Poehl—a fact which indicates that it is not specific to the testis—it is a ubiquitous constituent of the whole organism, in the female as well as the male.

Testicular preparations, including spermin, have been recommended in a host of disorders, particularly tabes, neurasthenia, melancholia, impotence, and paralysis agitans; in several cutaneous disorders, eczema and psoriasis; in disorders of nutrition, gout, obesity, and glycosuria; but others again have failed to obtain any favorable results. Spermin has also been recommended by Poehl and his followers not only in the majority of the foregoing disorders, but in many others besides, in acne, rheumatism, syphilis, marasmus, and in various infections, such as typhoid fever, diphtheria, and even cholera. It has been tried in Addison's disease, but adrenal preparations are to be preferred.

In the light of the analysis submitted above, however, there is good ground for the belief that beneficial effects were obtained in all these maladies. That the nucleo-albumins of orchitic extract acting as would glycerophosphates could be beneficial in the disorders enumerated, no one can deny. This can hardly be said, however, of the cutaneous and nutritional disorders, unless the spermin the extract contains, by enhancing oxidation and the destruction of toxic wastes, proves to be the active agent. Spermin itself—as adrenoxidase—is unquestionably capable of doing this actively, and in syphilis and marasmus to markedly enhance the functional activity of all tissues. Again, the beneficial rôle of spermin in infections finds its explanation in a fact I have repeatedly emphasized, viz., that the oxygenized adrenal secretion, the active agent of spermin, from my viewpoint, is an active participant in all immunizing processes, local and general. The main point to determine, however, is whether orchitic extract, or spermin, affords better or as good results in any of the disorders enumerated than other remedies at our disposal. The evidence available indicates that such is not the case.

KIDNEY ORGANOTHERAPY.

That the kidneys produce an internal secretion is still problematic. Brown-Séquard, having removed the kidneys and caused uræmia, found that the injection of a glycerin extract of kidney prolonged the life of the animals as compared to those in which the same operation was not followed by the use of the kidney extract. This experiment, which has been repeated by others, forms the basis of the belief that the kidney produces an internal secretion. That such a conclusion may not be warranted is suggested by the fact that the kidneys, along with some of the organs so far reviewed, are also rich in adrenal tissue—the so-called "adrenal rests" from which hypernephroma sometimes develops—and that as such they are capable, as an active factor in the immunizing functions of the body, of counteracting temporarily the toxæmia or "uræmia" brought on by removal of the kidneys. Indeed, the relief afforded is but ephemeral, death being postponed but one to two days in rabbits, in which Bitzou[147] repeated Brown-Séquard's experiments. Dromain and de Pradel Bra[148] had also noticed that injections of kidney extract lessened the fits of epilepsy, another toxæmia. Dubois[149] and Renaut[150] have also found that kidney extracts were endowed with antitoxic power.

That we are again dealing mainly with a manifestation of the adrenal principle is further suggested by its powerful blood-pressure-raising property. Tigerstedt and Bergman found that rennin possessed this power; Bingel and Strauss[151] recently confirmed their observation, and found that its action corresponded with that of adrenal and pituitary extracts, those of other organs causing depressor effects. The rise of pressure produced by kidney extract was high, *i.e.*, from 40 to 60 mm. Hg, and lasted from fifteen to thirty minutes. The authors concluded, moreover, that "the action of rennin, like that of adrenalin, is exerted in the muscles of the peripheral vessels." Its general action, however, is more like that of pituitary body extract, the adrenal principle being doubtless combined organically, as in the pituitary, with bodies which prolong and perhaps control advantageously the action of the former. Like adrenal preparations kidney extract produces dilatation of the pupil. This sustains my opinion that its action is due to adrenal principle.

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[147] Bitzou: Jour. de physiol. et de path. géner., Nov. 15, 1901.

[148] Dromain and de Pradel Bra: C.-r. heb. des sci. et mém. de la Soc. de Biol., Paris, 1896.

[149] Dubois: Soc. de Biol., p. 287, 1903.

[150] Renaut: Bull. gén. de thérap., T. 147, pp. 3 and 37, 1904.

[151] Bingel and Strauss: Deut. Archiv f. klin. Med., xcvi, S. 476, 1909; July 26, 1896.

Even the oxidizing power I have attributed to the adrenal secretion seems to be reproduced; Batty Shaw,[152] who also finds "very little justification for the existence of an internal secretion" in the kidney, remarks that "possibly nephrin and other renal preparations provide a means of stimulating oxidation in general, the kidney merely sharing in this oxidation"—a very accurate estimate from my viewpoint. Shaw adds, moreover, that "similar good results have been reported as a result of treatment by means of spermin and testicular extract," both of which, as I have shown, also owe, in all probability, their therapeutic effects to the adrenal principle they contain.

The *therapeutic application* of kidney preparations has received considerable attention, and favorable results have been reported in about one-half of the cases of chronic nephritis, or Bright's disease, in which it was tried. The mode of action, in the light of the facts submitted above, is mainly an increase of the antitoxic power of the blood and diminution, therefore, of the irritation of renal apparatus. Page and Dardelin,[153] for example, report marked amelioration in 18 cases, using a maceration prepared as follows: A very fresh kidney from a pig is cut into minute pieces, washed with fresh water to remove the excess of urine, then hashed and pounded into pulp. This pulp is put into 300 grammes (9 ounces and 5 drachms) of fresh water to which the physiological proportion of salt, 7.50 to 1000, has been added. It is then allowed to macerate for three hours, stirred occasionally, and kept in a cool place to avoid fermentation. The red water of the maceration is divided into three parts to be drunk by the patient during the day. It is more conveniently given, however, in tablet form, as "nephritin" prepared in this country by Reed and Carnrick. Only the active substance of the kidney is used in this preparation, the dose being from 10 to 15 5-grain (0.33 Gm.) tablets daily in divided doses, given between meals.

Kidney preparations have also been used with more or less advantage in puerperal intoxications and epilepsy, but their field is essentially the various forms of nephritis, and particularly for the prevention of uræmia. They also tend to increase diuresis and reduce the albumin. As stated above, however, favorable effects are to be expected in about one-half of the cases.

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[152] Shaw: *Loc. cit.*, p. 216.
[153] Page and Dardelin: Presse médicale, Dec. 21, 1904.

MAMMARY GLAND ORGANOTHERAPY.

It is held by some that the mammary gland produces an internal secretion, but what evidence there is on the subject is so weak that it can hardly be taken into account. Introduced by Bell, of Glasgow, and in this country by the late John H. Shober, it has shown therapeutically marked stimulating action upon the uterus, but the manner in which it produces this effect has remained obscure. An extract lowers somewhat, and but temporarily, the blood-pressure and the pulse. According to Shober, it diminishes the blood supplied to the uterus and thus controls hæmorrhage, its action resembling that of ergot, though free of the unpleasant effects of the latter drug. From my viewpoint, therefore, it would act by causing constriction of the arterioles.

Mammary gland is prepared in the form of a tablet made of the desiccated gland of the sheep, each tablet representing 20 grains (1.32 Gm.) of the fresh gland. The dose is from 3 to 6 tablets daily.

The *therapeutic application* is restricted to the genital apparatus. In cases of uterine fibroids characterized by excessive menorrhagia and metrorrhagia the bleeding was found by Shober to be controlled in a few weeks and the periods become regular, normal, and free from pain. There is improvement in the patient's health and weight, and the tumors themselves diminish in size up to a certain point. The patient is thus placed in a better condition for any needed operation, and often the necessity for an operation is postponed. Where there is evidence of inflammatory or degenerative changes, or when serious pressure symptoms are not controlled after a reasonable trial, operation should not be delayed. In 43 cases of uterine fibroma treated by Fedoroff, cure is claimed to have been obtained in 33, while there was a marked reduction of the growth in 43 per cent. Pozzi has advocated its use in uterine hæmorrhage of any kind attending metritis. Briggs[158a] found it effective in the menorrhagia of uterine fibroids in 10 gr. (0.66 Gm.) doses three times a day.

[158a] Briggs: Endocrinology, April, 1917.

Mammary gland has also been recommended to assist uterine involution and to enhance lactation. But the reports on the use of this agent have been antagonistic.

THYMUS ORGANOTHERAPY.

In the sixth chapter (p. 280), I submitted the experimental and clinical evidence which led me to suggest, in 1907, that the function of the thymus was to supply an excess of phosphorus in organic combination during the growth of the body, *i.e.*, particularly while the development of the osseous and nervous systems demanded such a reserve. This was sustained by the recognized fact that certain diseases of children and adolescents, especially marasmus, rachitis, and trophic disorders of the brain and nervous system, were due, in part, to the functions of the thymus. While it cannot be affirmed that this theory actually represents the function of the organ—the thymus having been the graveyard of many hypotheses—all that can be said for it is that it seems to account for the clinical results obtained under its use better than any hypothesis so far advanced, besides corresponding with the laboratory findings of its effects.

DISEASES OF THE THYROID.—In simple goiter it was first tried by Mikulicz,[154] who obtained sufficiently favorable results in 5 out of 11 cases to render operation unnecessary, at least for the time being. Reinbach[155] considers it probably superior to thyroid because the unpleasant effects of the latter are avoided; for the same reason it is especially suitable when organotherapy has to be used continuously. This view is based on the employment of thymus in a large number of cases in the Breslau clinic. Mikulicz gave from 2½ to 4 drachms (10 to 16 Gm.) of the raw sheep thymus on bread three times a week, increasing the dose to 7 drachms (28 Gm.) if required.

We have seen that in exophthalmic goiter it had proven efficacious in the hands of Owen[156] in advanced cases, and also in those of Maude[157] when other remedies had been used fruitlessly. The latter gave 45 grains (3 Gm.) daily to a severe case, which greatly improved, relapsing whenever the treatment was interrupted. S. Solis-Cohen[158] also advocates its use in this disease, having found that it exerted its beneficial influence mainly upon the nervous symptoms of the disease without affecting the exophthalmus. Huston White[159] found that the nervous symptoms were alone improved.

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[154] Mikulicz: Berlin. klin. Woch., Bd. xxxii, S. 342, 1895.
[155] Reinbach: Mittheil. aus den Grenzgebiet. d. Med. u. Chir., B. i, S. 262, 1896.
[156] Owen: Brit. Med. Jour., Oct. 10, 1896.
[157] Maude: London Lancet, July 18, 1896.

These observations coincide with my own view of the manner in which thymus gland produces its beneficial effects. The excess of thyroiodase produced in exophthalmic goiter causes, we have seen, too rapid oxidation of the phosphorus in organic combination in the tissues, particularly in those of the nervous system which are extremely rich in phosphorus. Thymus, supplying phosphorus in organic combination, replaces that lost by the nervous system, thus procuring marked benefit in this one direction. As 5 grains (0.33 Gm.) of the dried thymus are equivalent to 30 grains (2 Gm.) of the fresh gland, this dose can readily be given three times daily.

RACHITIS, OR RICKETS.—The same explanation, *i.e.*, the purveying of phosphorus in organic combination—to the osseous system, in the present connection—accounts for the undoubted benefit thymus has procured in this disorder. Mendel,[160] having used thymus gland in 1½ to 3 drachms (6 to 12 Gm.) daily in over 100 cases, obtained marked benefit in a large proportion, but especially in the nervous symptoms, including spasm of the glottis. It had previously been tried by Stoppato,[161] but without marked benefit. In Mendel's cases both fresh and commercial tablets were tried, the cases being subdivided as follows: 1, those which showed prodromal symptoms only; 2, those in which deformity of the osseous system was the chief feature; 3, those marked by spasm of the glottis, and, 4, those in which splenic enlargement was the most important sign. Marked improvement was noted in all after from three to four weeks, and dentition and the closure of the fontanelle proceeded satisfactorily. No untoward symptoms were noted—a marked advantage over thyroid preparations. In a case of stunted growth, obviously of osseous origin, in a boy of 14 years, R. Webb Wilcox[162] obtained 9¼ inches growth in three years by the persistent use of 2 grains (0.13 Gm.) thymus night and morning.

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[158] Solis-Cohen: Jour. Amer. Med. Assoc., Aug. 18, 1900.
[159] White: Brit. Med. Jour., vol. i, p. 786, 1899.
[160] Mendel: Münch. med. Woch., Bd. xlix, S. 134, 1902.
[161] Stoppato: Policlinico, April 15, 1897.
[162] Wilcox: Boston Medical and Surgical Journal, Aug. 13, 1903.

The view that these effects are due to the addition of phosphorus in organic combination to the body is further sustained by the results of experimental observation by Hart and Nordmann,[163] that the thymus had a definite relation to assimilation, and that it took an active part in the resistance of the organism to infection. As I will show in the second volume, page 878, nucleo-proteid, in so far as its phosphorus in organic combination is concerned, is an active participant in the immunizing process.

BRAIN AND NERVE SUBSTANCE ORGANOTHERAPY.

While these agents have given good results, the theory that brain and nerve substance possess or produce an internal secretion has never been sustained scientifically.

The clinical results, though quite discordant, particularly in the neuroses and psychoses in which these preparations have been tried, have shown a tendency to harmonize since the introduction by Sciallero[164] of an oily extract. Page,[165] who has obtained unusually good results in neurasthenia by means of injections of this extract, ascribes them to its antitoxic and antispasmodic effects. Wassermann and Takaki had previously shown that tetanus toxin was neutralized by contact with brain substance, and that when a fatal dose of tetanus toxin was injected with brain substance the fatal effects were prevented. The same observations were made in the case of hydrophobia by Babes; in strychnine and morphine poisoning by Widal and Nobécourt; in tetanus by Krokiewicz; in epilepsy by Lion and also Kaplan, using Poehl's opocerebrin—in accord with Dana's experience several years earlier. Sciallero, who obtained encouraging results in neurasthenia, hysteria, chorea, tic, and epilepsy, used his oily extract "cephalopin" in doses varying from 1 to 5 c.c. (16 to 81 minims). No untoward effects were obtained.

Although it is very improbable that brain extracts injected into the tissues act as they do in the test-tube, it seems established that they act much as do the lecithins on the market, *i.e.*, by furnishing phosphorus to the organism in an assimilable form, or as nucleo-proteids in enhancing the immunizing process. Be this as it may, these substances seem to have produced effects which suggest that they are worthy of further study.

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[163] Hart and Nordmann: Berlin. klin. Woch., May 2, 1910.
[164] Sciallero: 'Riforma Medica, Jan. 27, 1904.
[165] Page: C.-r. de l'Académie de Méd., March 30, 1909.

THE PINEAL GLAND ORGANOTHERAPY.

The functions of this organ have not as yet been determined to any degree. It is no longer regarded as a purely vestigial structure, however, tumors of the pineal as noted by Marburg[166] and others being capable of causing obesity, while Ogle, Frankl Hochwart,[167] and other clinicians have recorded marked precocity in young subjects, as to stature, genital development, and hair growth. These effects have also been ascribed to a secretory function, but the results obtained from extracts of the gland have been contradictory, though these agents appeared to increase the strength of the heart-beat.

A kinship with the functions pituitary is suggested by many facts. From my viewpoint, it does not possess the characteristics of a secreting gland but, seemingly, those of a nervous organ working in harmony with the pituitary body, through fibers which meet those originating from the latter organ, in the region of and in the corpora quadrigemina. The fact noted by Biedl[168] that in the adult animal the organ is "a negligible quantity" sustains my view, since a co-ordinating center can be sacrificed without permanent harm more readily than a secreting organ whose product should, as in the present case, deeply influence metabolism, if the effects of organic lesions of the organ are taken as standard.

As a therapeutic agent, Dana and Berkeley[169] claim to have obtained improvement in backward children owing to its stimulating influence on general metabolism.

HORMONE THERAPY.

The word "hormone" was applied by Starling to the group of substances secreted by various organs—the ductless glands in the group studied in this work—which could enhance the functions of other organs. Precisely as I had held three years earlier

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[166] Marburg: Deutsch. Zeitschr. für Nervenheilk., B. xxxvi, S. 112, 1908.
[167] Frankl Hochwart: *Ibid.*, B. xxxvii, S. 455, 1909.
[168] Biedl: The Internal Secretory Organs, p. 255, 1912.
[169] Dana and Berkeley: Medical Record, May 10, 1912.

(the adrenal secretion exciting the thyroid, the pituitary, the pancreas, etc.); these hormones were shown by Starling to reach the distant structures they influenced, through the intermediary of the blood.

While certain hormones influence various organs, others affect only one organ or a system of them. Bayliss and Starling termed "secrétin" a hormone formed in the duodenal mucous membrane under the influence of hydrochloric acid from the stomach. Carried by the circulation to the intestinal mucosa, the pancreas, and the liver, it activates the production of the secretions produced by these organs. As I suggested in 1907 (see vol. ii, p. 861), this hormone presents several properties of adrenal extractives.

Another hormone has been obtained from the gastric mucosa by Zuelzer, Dohrn, and Marxer[170] which has been found to enhance peristalsis. It being impossible to obtain it in sufficient quantities from the stomach, it was sought elsewhere, and was found in ample quantities in the spleen—that junkshop in which red corpuscles (which, as I suggested in 1903, are the common carriers of the adrenal principle) are broken up along with other cells. This splenic hormone specifically stimulates intestinal peristalsis to a degree so remarkable that the intestinal movements in the experimental animal may be shown cinematographically ten to fifteen minutes after an intravenous injection. The use of liquid preparations of the posterior pituitary (*q.v.*) has, however, advantageously superseded it for the same purpose, being more lasting and less violent.

PLURIGLANDULAR THERAPY.

The simultaneous use of two or more glandular products, sometimes in conjunction with drugs, has been found advantageous in many disorders. This feature of the subject as a whole will be considered at the end of the second volume, in a supplement in which all diseases benefited by such treatment will be arranged alphabetically.

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[170] Zuelzer, Dohrn, and Marxer: Berl. klin. Woch., Nu. 46, 1908.

INDEX TO VOLUME FIRST.

See also the Second Volume Index and the Supplement which follows it for additional diseases, and also for an indexed list of all diseases referred to in both volumes.

Aberrant exophthalmic goiter. See Hyperthyroidia, 212.
Abortion, 25.
  habitual, corpus luteum in, 780.
Abscess, adrenal apoplexy in, 20.
Accelerator cardiac phenomena, 445.
Accessory thyroid glands, 271.
  adrenals, 55.
Achondroplasia, 205.
Acne, spermin in, 782.
Acromegaly, 607.
  asthenic stage, 613.
  pathogenesis, 608.
  pathological anatomy of, 516.
  pathology of, 616.
  pituitary in, 512, 514, 771.
  sthenic stage of, 610.
  symptomatology of, 512, 515, 608.
  treatment of, 618.
Addison's disease, 97.
  adrenal apoplexy in, 19, 20.
  adrenal gland in, 105, 764.
  grafting in, 108.
  pathogenesis of, 99.
  pituitary gland in, 770.
  posterior pituitary body in, 514.
  spermin in, 782.
  symptomatology of, 99.
  treatment of, 108.
Adenoma, hæmorrhagic, of the adrenals, 138.
Adenomatous goiter, 261.
Adiposis dolorosa, thyroid gland in, 727.
Adipositas cerebralis, 307.
  treatment of, 309.
Adolescent heart, 11.
Adrenal apoplexy, 19, 20.
    in abscess, 19.
    in Addison's disease, 19.
    in arteriosclerosis, 19.
    in dysentery, bacillary, 19.
    in epilepsy, 19.
    in meningitis, 19.
Adrenal apoplexy in pneumonia, 19.
    in purpura, 19.
    in renal diseases, 19.
    in tuberculosis, 19.
  cortex, 50.
  extract, 750.
  hæmatoma, 126.
    diagnosis of, 128.
    pathogenesis of, 126.
    prognosis of, 129.
    symptomatology of, 126.
    treatment of, 129.
  hæmorrhage, 116.
    and acute hyperadrenia, 116.
    diagnosis of, 123.
      in adults, 121.
      in the child, 123.
      in the infant, 123.
    pathogenesis of, 118.
      in adul' 121.
      in children, 120.
      in the newborn, 118.
    prognosis of, 124.
    symptomatology of, 118.
      in adults, 121.
      in children, 120.
      in the newborn, 118.
    treatment of, 124.
  hæmorrhagic pseudocyst, 126.
  insufficiency, 80. (See *Hypoadrenia.*)
  overactivity, glycosuria as a symptom of, 362.
  preparations, general indications of, 764.
  rests, 57.
  secretion a constituent of hæmoglobin, 63.
    action on heart muscle, 433.
    and functional activity, 359.
    as a factor of temperature, 66.
    as source of the functional activity of the right heart, 421.

Adrenal secretion distributed by the red corpuscles as oxidizing agent, 65.
  in cerebrospinal plasma-channels, 573.
  in its relation to respiratory functons, 453.
  in metabolism, 59.
  in pulmonary functions, 421. (See also *Adrenals*.)
  in pulmonary respiration, 59.
 subsidiary, 55.
 stigmata of insufficiency in idiocy, 300.
  of excessive activity in idiocy, 301.
 system, in cardiac functions, 421.
  and generative glands, 473.
  and the kidneys, 467.
  as the foundation of immunity, 620.
 tissues, subsidiary, 55, 57.
Adrenalin, 751.
Adrenals, increased functional activity of the, as cause of adrenal hæmorrhage, 25.
 blood-supply of the, 53.
 cancer of the, 137.
  diagnosis, 140.
  symptoms, 138.
  treatment, 141.
  varieties of, 137.
 diseases of the, 45.
 failure of, as cause of disease, 352.
 functions of the, 45.
 governing center of the, 71.
 hæmatomata of, 126.
 hæmorrhage into, 116.
 histology of the, 48.
 in ascites, 17.
 in chloroform anæsthesia, 8.
 in general infections, 18.
 in heart disease, 8.
 in idiocy, 297.
 in immunity, 622.
 in mental deficiency, 277.
 in pulmonary disorders, 12.
 in renal disorders, 15.
 in serous effusions, 17.
 in their relation to disease and treatment, 2.
  and respiratory chemism, 453.
 lymphatics of the, 54.
 malignant hypernephroma of the, 131, 133.
 nervous supply of, 54.
 spleno-adrenal communicating filaments, 415.
Adrenals, origin and structure of the, 45.
 sarcoma of, 137.
 stigmata of deficient activity of, in idiocy, 300.
 structure of, 45.
Adrenoxidase, 67.
 blood-platelets as droplets of, 64.
Adults, adrenal hæmorrhage in, 121.
  diagnosis of, 123.
 functional hypoadrenia in, 85.
  prophylaxis and treatment of, 94.
Adynamia, general, thyroid gland in, 710.
Alcohol, action of, on neurons, 522.
Alcoholic insanity, neurons in, 590.
Alopecia, 24.
 thyroid gland in, 734.
Amaurotic family idiocy, 303.
Amblyopia in acromegaly, 515.
Amenorrhœa, corpus luteum in, 779.
Amyloid liver, 43.
Amyotrophic lateral sclerosis and acromegaly, 515.
Anæsthesia as a symptom of acromegaly, 514.
 retraction of neuron-gemmules during, 521, 578.
Anthrax, suprarenal gland in, 19.
Anuria, suprarenal gland in, 15.
Apáthy's neuro-fibrils as plasma-channels, 540, 544, 568.
Appetite, excessive, as a symptom of acromegaly, 512.
 in glycosuria, 363.
Arrhythmia, 11.
Arteriosclerosis, adrenal apoplexy in, 20.
Arthritis, pituitary gland in, 775.
Arthritis deformans, thyroid gland in, 27.
Ascites, 17.
 suprarenal gland in, 17, 762.
Asphyxia, adrenal gland in, 765, 764.
Asiatic cholera, 18.
 suprarenal gland in, 18.
Assimilation, neutrophile leucocytes in, 654.
Asthenia, neuro-cardiac, 11.
Asthma, adrenal gland in, 14, 761, 765.
 bronchial, 14.
 pituitary gland in, 775.
 thyroid gland in, 710.
  suprarenal gland in, 14.
Augmentor cardiac phenomena, 449, 452.

- Auricular fibrillation, suprarenal gland in, 11.
  - flutter, suprarenal gland in, 12.
- Axis-cylinders as plasma-channels, 543.

- Backward child, 309.
  - diagnosis and pathogenesis, 310.
  - pineal gland in, 879.
  - pituitary gland in, 774.
  - treatment of, 311.
- Bacterial infection, adrenal gland in, 764.
- Bacterins, 696.
- Basedow's disease, 214. (See *Exophthalmic goiter.*)
  - incomplete, 212. (See *Hyperthyroidia.*)
- Basophile leucocytes, 680.
- Benign hypothyroidia, chronic, 175. (See *Hypothyroidia.*)
- Bilirubin, formation of, 360.
- Blood-pigments, hepatic, 360.
- Blood-platelets as droplets of adrenoxidase, 64.
- Blood-supply of the adrenals, 53.
- Bone necrosis, thyroid gland in, 711.
- Brain and cord, minute circulation of, 562.
  - and nerve substance organotherapy, 788.
  - extract, 788.
  - lower, identity of, 483.
  - neuroglia-fibers as the capillary system of, 582.
- Bright's disease, kidney in, 784.
- Bromides, action of, on neurons, 523.
- Bronchocele, 243.
- Bronchopneumonia, pituitary gland in, 770.
  - suprarenal gland in, 19.
- Bronzing, a symptom of advanced adrenal insufficiency, 515.
- Bulimia as a symptom of acromegaly, 512.
  - in glycosuria, 362.

- Cachexia parathyreopriva, 741. (See *Hypoparathyroid tetany.*)
- Cancer, adrenal gland in, 757.
  - of the adrenals, 137.
    - diagnosis of, 140.
    - symptoms of, 138.
    - thyroid gland in, 729.
    - treatment of, 141.
- Capillary hæmorrhage, adrenal gland in, 765.
- Cardiac disorders, adrenal gland in, 758, 765.
  - asthenic, adrenal gland in, 765.
    - pituitary gland in, 767.
- Carotid glands, 55.
- Catarrhal disorders, 24.
- Cephalopin, 788.
- Cerebrospinal substance, minute circulation of, 562.
- Childhood, functional hypoadrenia of, 83.
  - prophylaxis and treatment of, 92.
- Children, adrenal hæmorrhage in, 120.
  - diagnosis of, 123.
- Chloroform, action of, on neurons, 523.
  - anæsthesia, 8.
    - heart-failure in, suprarenal gland in, 8.
- Cholera, Asiatica, 18.
  - spermin in, 782.
  - suprarenal gland in, 18.
- Choleraic diarrhœa, 18.
  - suprarenal gland in, 18.
- Chorea, cephalopin in, 788.
  - pituitary extract in, 773.
- Chromaffin system, 45.
- Chronic constipation, hormone therapy in, 790.
- Cirrhosis of the liver, atrophic, etiology of, 347.
  - alcoholic, etiology of, 347.
  - portal, 41.
    - treatment, 43.
- Coccygeal body, 56.
- Collapse, adrenal gland in, 754, 764.
  - from hæmorrhage, adrenal gland in, 764.
- Colloid goiter, 260.
- Congenital goiter, 272.
- Constipation, chronic, hormone therapy in, 790.
- Constrictive goiter, 262.
- Cord, minute anatomy of, 562.
  - neuroglia-fibers as the capillary system of, 583.
- Corpus luteum, 479.
  - extract, 777, 779.
- Cortex of the adrenals, 50.
- Cretinism, 193.
  - endemic, 196.
  - etiology, 196.
  - pathogenesis of, 193.
  - pathology of, 198.
  - posterior pituitary body in, 514.
  - sporadic, 197.
  - symptomatology of, 193.

Cretinism, thyroid gland in, 710.
  treatment of, 198.
Cretinoid idiocy, 197.
  pachydermia, 197.
Cystic goiter, 261.
Cysts, hæmorrhagic, 261.

Deafness as a symptom of acromegaly, 513.
Degenerative goiter, 259.
  hypothyroid goiter, 259.
Delusions as a symptom of acromegaly, 512.
Dementia præcox, 30, 325.
  symptomatology, early, 339.
  treatment, 341.
    lecithins in, 342.
    nucleinates in, 342.
    thymus gland in, 342.
Dercum's disease, thyroid gland in, 727.
Dermatitis herpetiformis, thyroid gland in, 734.
Diabetes mellitus, 36. (See also *Glycosuria.*)
    treatment, 38, 39, 40.
  asthenic phase, 37, 40.
    hypophysis sicca in, 40.
    pancreatic substance in, 40.
    pancreatin in, 40.
  sthenic phase, 37.
Diabetes insipidus, 40.
  hypophysis sicca in, 41.
Diabetic coma, 363.
Diarrhœa, choleraic, 18.
  suprarenal gland in, 18.
Digestive apparatus. (See *Intestines*, *Liver*, *Pancreas*, and *Stomach.*)
Diphtheria, pituitary gland in, 770.
  spermin in, 782.
Dysentery, bacillary, adrenal apoplexy in, 19.
Dysfunction of the internal secretions, disorders due to, 325.
Dysmenorrhea, corpus luteum in, 779.
Dyspnœa as a symptom of acromegaly, 513, 515.
Dystrophia adiposo-genitalis, 307.
  treatment of, 309.

Eclampsia, thyroid gland in, 710.
Eczema, 24.
  chronic, thyroid gland in, 734.
  of young children, thyroid gland in, 734.
  testicular extract in, 782.
Effusions, adrenal gland in, 17, 762.
Endemic cretinism, 198.
Endocarditis, 32.
  etiology of, 345.
  pathogenesis, 33, 34, 35.
  treatment, 35.
Enuresis, 24.
  thyroid gland in, 733.
Eosinophile leucocytes, 667.
Epilepsy, adrenal apoplexy in, 20.
  as manifestations of excessive motor activity, 508.
  brain substance in, 788.
  cephalopin in, 788.
  kidney gland in, 783, 784.
  opocerebrin in, 788.
  thyroid gland in, 710, 716.
Epinephrin, 751.
Erysipelas, pituitary gland in, 770.
  suprarenal gland in, 19.
  thyroid gland in, 738.
Erythromelalgia in acromegaly, 515.
Exanthemata, thyroid gland in, 711.
Exophthalmic goiter, 214.
    aberrant, 175. (See *Hypothyroidia.*)
    asthenic or myxœdematous stage of, 222.
    enlarged thymus as complicating factor of, 223.
    etiology of, 227.
    larval, 212. (See *Hyperthyroidia.*)
    myxœdematous stage of, 222, 237.
    operative risks and results in, 241.
    pathogenesis of, 216.
    pituitary gland in, 772.
    posterior pituitary body in, 514.
    sthenic or first stage of, 217.
    surgical treatment of, 238.
    symptomatology of, 216.
    thymus gland in, 786.
    transition stage of, 221, 222, 237.
    treatment of, 233.

Febrile infections, thyroid gland in, 738.
Fever, genesis of, 628.
  internal secretions in, 630.
  leucocytes in, 620.
Fibrous goiter, 261.
Fœtal rickets, 205.
Foramina Thebesii in cardiac functions, 421, 441.
Forme fruste de la maladie de Basedow, 212. (See *Hyperthyroidia.*)
Fractures, thyroid gland in, 710.
Fröhlich's disease, 307.
  treatment of, 309.
Functional activity of the brain *versus* retraction of the neuron-gemmules, 577, 578.

- Functional activity of the right heart, adrenal secretion as the source of, 421.

- Gangrene, gaseous, suprarenal gland in, 19.
- Generative glands, adrenal system and, 473.
- Gerlach's fibers as plasma-channels, 568.
- Gigantism, 607.
- Glycogen and its formation, 361.
- Glycosuria, 35. (See also *Diabetes.*)
  - as a symptom of adrenal insufficiency, 365.
  - as a symptom of adrenal overactivity, 362, 366.
  - as a symptom of excessive formation of dextrose, 367.
  - coma in, 363.
  - drugs as a cause of, 362.
  - non-converted sugar and, 366.
  - pituitary and, 76.
  - ptyalin and, 418.
  - testicular extract in, 782.
  - treatment, 38.
- Goiter, 243.
  - adenomatous, 261.
  - colloid, 260.
  - congenital, 272.
    - symptoms of, 272.
    - treatment of, 273.
  - constrictive, 262.
  - cystic, 261.
  - degenerative, 259.
    - operative risks and results of, 269.
    - surgical treatment of, 266.
    - symptoms, 263.
    - treatment, 265.
  - etiology of, 244.
  - exophthalmic, 214. (See *Exophthalmic goiter.*)
  - fibrous, 621.
  - hæmorrhagic, 262.
  - hyperthyroid or toxic, 258.
    - treatment of, 258.
  - hypothyroid degenerative, 259.
    - treatment of, 265.
      - surgical, 266.
  - in the newborn, 272.
  - inflammation of a, 274. (See *Strumitis.*)
  - intrathoracic, 261.
  - lingual, 263.
  - malignant, 270.
    - treatment of, 271.
  - simple hypothyroid non-toxic, 248.
    - pathology of, 251.
- Goiter, simple hypothyroid non-toxic, prognosis of, 251.
    - treatment of, 251.
  - thyroid gland in, 728.
  - varieties of, 247.
- Goitrous accessory glands, 271.
- Golgi's fibers as plasma-channels, 568.
- Gonorrheal arthritis, pituitary gland in, 775.
- Gout, testicular extract in, 782.
- Graafian follicles, 480.
- Graves's disease, 214. (See *Exophthalmic goiter.*)
- Growth, stunted, pituitary gland in, 773.

- Hæmatoma, adrenal, 126.
- Hæmoglobin, adrenal secretion a constituent of, 63.
    - as the oxidizing agent of the, 60.
  - dissociation of, in glycosuria, 365.
  - formation of, 360.
- Hæmophilia, thyroid gland in, 736.
- Hæmoptysis, pituitary gland in, 776.
- Hæmorrhage, adrenal, 116.
    - adrenal gland in, 755, 765.
  - of genital system, pituitary gland in, 769.
- Hæmorrhagic adenoma of the adrenals, 138.
  - adrenal pseudocyst, 126.
  - cysts, 261.
  - goiter, 262.
- Hair, coarseness of, and adrenal insufficiency, 515.
- Haller's fibers as plasma-channels, 568.
- Hay fever, adrenalin ointment in, 762.
- Headache, pressure as a source of, 512.
- Heart, accelerator phenomena of, 445.
  - adrenal secretion in functions of, 421, 433.
  - augmentor phenomena of, 449.
  - diseases and treatment of, 8.
    - adolescence, 11.
    - acute infections, 11.
    - acute myocarditis, 345.
    - arrhythmias, 11, 12.
    - asthenia, neuro-cardiac, 11.
    - auricular fibrillation, 11.
    - auricular flutter, 12.
    - chloroform failure, 8.
    - endocarditis, 33, 345.
    - failure of, 8, 9, 109, 768.
    - heart-block, 12.
    - hypertrophy, 512.
    - irritable, 11.

Heart, diseases and treatment of, palpitations, 512, 515.
    pericarditis, 35.
    senile, 9.
    surgical, 755, 758, 764.
    valvular disease, 345.
  foramina Thebesii in, 421, 441.
  functional mechanism of, 452.
  inhibitor phenomena of, 446, 452.
  innervation of, 444.
  leucocytes and nutrition of, 441.
Hepatic disorders. (See *Liver.*)
Hip-joint disease, thyroid gland in, 737.
Histology of adrenals, 48.
Hormone therapy, 789.
Hyaline cells, 652.
Hydrophobia, brain substance in, 788.
Hyperadrenalism, 115.
Hyperadrenia, 115.
  acute, 116.
Hyperæmia, thyroid, 206.
Hyperæsthesia, the posterior pituitary body and, 512.
Hyperemesis gravidarum, corpus luteum in, 780.
Hypernephroma, 129.
  diagnosis of, 132, 134.
  malignant, of the adrenals, 131; 133.
  of the kidneys, 132.
  pathogenesis of, 130.
  pathology of, 136.
  prognosis of, 137.
  symptomatology of, 130.
  treatment of, 137.
Hyperthermia, 344.
Hyperthyroid or toxic goiter, 253.
Hyperthyroidia, 212.
Hyperthyroidism, 212. (See *Hyperthyroidia.*)
Hypertrophic rosacea, thyroid gland in, 735.
Hypoadrenalism, 80.
Hypoadrenia, 80.
  chronic progressive, 97. (See *Addison's disease.*)
  functional, 82.
    in the adult, 85.
      prophylaxis and treatment of, 94.
    in childhood, 83.
      prophylaxis and treatment of, 92.
    of infancy and childhood, 83.
      prophylaxis and treatment of, 90.
    of old age, 88.
      prophylaxis and treatment of, 94, 96.
    prophylaxis of, 89.
Hypoadrenia, functional, treatment of, 89.
  terminal, 109.
    pathogenesis of, 110.
    pathology of, 111.
    symptomatology, 110.
    treatment, 112.
Hypoparathyroid tetany, 741.
    non-operative, 743.
    post-operative, 742.
    symptomatology of, 742.
    treatment of, 744.
Hypoparathyrosis, 741. (See *Hypoparathyroid tetany.*)
Hypophysis. (See *Pituitary.*)
Hypothyroid degenerative goiter, 259.
  non-toxic goiter, simple, 248.
Hypothyroidia, 175.
  etiology of, 183.
  larval type, 24.
  pathology of, 183.
  progressive, 185. (See *Myxœdema.*)
  symptomatology of, 177.
  treatment of, 184.
Hypothyroidism, 175. (See *Hypothyroidia.*)
Hysterectomy, corpus luteum after, 779.
Hysteria, cephalopin in, 788.

Ichthyosis, thyroid gland in, 734.
Idiocy, 277.
  adrenals in, 297.
  amaurotic family, 303.
    treatment, 306.
  and disease of the pituitary bodies, 513.
  cretinoid, 197.
  Mongolian, 289.
    etiology and pathogenesis of, 292.
    pathology of, 294.
    treatment of, 295.
  myxœdematous, 197.
  pituitary gland in, 773.
  stigmata of adrenal insufficiency in, 300.
    of the adrenal cortex, 300.
    of excessive activity of the adrenal cortex in, 301.
Immunity, 698.
  adrenal system in, 626.
  adrenals in, 622.
  internal secretions in, 628.
  kidneys in, 473.
  leucocytes in, 690, 691.
    in their relation to, 692.
  simplified theory of, 696.

Immunity, thyroparathyroid apparatus in, 142, 622.
Immunizing center, pituitary body as the seat of the, 684.
  mechanism, mode of action of the, 628.
Impotence, testicular extract in, 782.
Incomplete Basedow's disease, 212.
  myxœdema, 175.
Infancy, adrenal hæmorrhage in, 118, 123.
  functional hypoadrenia in, 83.
    prophylaxis and treatment of, 90.
Infantile generative organs, corpus luteum in, 780.
  myxœdema, 193.
Infantilism, Lorain type of, 204.
  Mongolian, 205.
  myxœdematous, 201.
Infections, general, and treatment of, 18.
    anthrax, 19.
    cholera, Asiatica, 18.
    choleraic diarrhœa, 18.
    dysentery, bacillary, 19.
    erysipelas, 19.
    gangrene, gaseous, 19.
    influenza, 19.
    malaria, pernicious, 19.
    measles, 19.
    pneumonia, 19, 20.
    scarlatina, 19.
    septicemia, 19.
    typhoid fever, 18.
Infectious diseases, pituitary gland in, 770.
  thyroid gland in, 711.
  treatment of, 351.
Influenza, 352.
  adrenal apoplexy in, 356, 357.
  etiology of, 352.
  pituitary gland in, 770.
  suprarenal gland in, 19.
  treatment, 356.
Infundibular extract, 767.
Inhibition, active, of heart due to excessive nervous stimulation, 446, 452.
Inhibitors of adrenal functions, toxins, poisons, venoms, and drugs in large doses as, 19.
Innervation of the heart, 444.
Insanity, alcoholic, neurons in, 590.
  the posterior pituitary body in, 612.
  thyroid gland in, 711.
Insufficiency of the adrenals, 89.
Internal secretions and organotherapy, 700.
Internal secretions, disorders due to dysfunction of, 325.
  in practice, 1.
  of the pancreas and spleen, 362.
  overactive, pathological effects of, 342.
Inter-renal tissues, subsidiary, 55, 57.
Interstitial gland, 480.
Intestinal occlusiôn, hormone therapy in, 790.
  paresis, pituitary gland in, 774.
    post-operative, hormone therapy in, 790.
Intestines, diseases of, 349.
  typhoid fever, etiology of, 349.
Intrathoracic goiter, 261.
Irritable heart, 11.

Jaundice, malignant, etiology of, 347.

Kidneys, adrenal system and the, 467.
  extract, 703, 728.
  hypernephroma of the, 132.
  organotherapy, 782.
  See also Renal Disorders.

Lactation, mammary gland extract in, 786.
Larval exophthalmic goiter, 212.
Lecithin as the active body of myelin, 534, 543.
Lépine's glycolytic ferment as oxidizing substance, 411, 412.
Leprosy, thyroid extract in, 785.
Leucocyte granulations as secretory products, 644.
Leucocytes, basophile, 680.
  classifications of, 650.
  eosinophile, 667.
  functional mechanism of, 639.
  granules in, 644.
  in immunity, 691.
    and fever, 620.
  neutrophile, 653.
    in assimilation, 654.
  physiological chemistry of, 647.
  relation to nutrition, organic functions, and immunity, 633.
Leucorrhea, 25.
Life, the pituitary bodies as co-centers in sustaining, 482.
Lingual goiter, 262.
Liver, blood-pigments of, 360.
  diseases and treatment of, 41.
    acute yellow atrophy of, 43, 347.
    amyloid, 43.
    cirrhosis, alcoholic, 347.
      atrophic, 347.

Liver, diseases and treatment of, cirrhosis, portal, 41.
jaundice, malignant, etiology of, 347.
hepatic artery, functional vessels of, 360.
hepatic cell-canaliculi, 361.
hepatic tissues in their relations to bacteria, 360.
general function of, 360.
minute anatomy of, 360.
pancreas and spleen, combined functions of, 360.
physico-chemical functions, 360.
Lorain type of infantilism, 204.
Lower brain, functions of, 483.
Lungs, adrenal system in functions of the, 421. (See also *Respiration.*)
disorders and treatment of, 12.
adrenals in, 12.
asthma, bronchial, 14.
pleurisy, 35, 346.
pneumonia, lobar, 12.
senile, 12.
tuberculosis, 20, 27.
innervation of, 454.
nervo-vascular mechanism of, 454.
Lupus, thyroid gland in, 735.
Lutein, 780.
Lymphatics of the adrenals, 54.
Lymphocytes and hyaline cells, 652.

Malarial fever, pernicious, suprarenal gland in, 19.
Malignant goiter, 270.
hypernephroma of the adrenals, 131, 133.
neoplasms, thyroid gland in, 711.
Mammary gland, 785.
Marasmus, spermin in, 782.
Measles, suprarenal gland in, 19.
Melancholia as a symptom of adrenal insufficiency, 513.
testicular extract in, 782.
Meningitis, adrenal apoplexy in, 20.
Menopause, corpus luteum extract in, 779.
ovarian extract in, 777.
thyroid gland in, 710.
Menorrhagia, pituitary gland in, 769.
Menstrual disorders, corpus luteum in, 779.
Mental backwardness in children, 277.
adrenals in, 277.
pituitary in, 277, 774.
thymus in, 277.
thyroid in, 277, 278.
prophylaxis of, 314.
Mental backwardness in children, prophylaxis of, cutaneous sensibility, 324.
hearing, 322.
senses, development of, in, 322.
smell, 323.
taste, 323.
vision, 323.
Mental diseases, 30.
pituitary gland in, 773.
phenomena of acromegaly, 512, 514.
Metabolic disorders and treatment of, 35.
diabetes mellitus, 36.
glycosuria, 35.
Metrorrhagia, 25.
pituitary gland in, 769.
Microsomes, 644.
Migraine, 24.
thyroid gland in, 710.
Mitoma, 633.
Mitral disorders, pituitary gland in, 768.
Mongolian idiocy, 289.
infantilism, 205.
Morphine, action on neurons, 520, 522.
poisoning, brain substance in, 783.
Motor areas of gray substance as sensory areas, 508.
Muscular atrophy in acromegaly, 514.
hypernutrition and adrenal overactivity, 512.
weakness and adrenal insufficiency, 513.
Myasthenia, pituitary gland in, 773.
thyroid gland in, 710.
bulbo-spinal, ovarian extract in, 773.
pituitary gland in, 773.
Myelin and the functional energy of nerves, 534, 536, 543.
Myocarditis, acute, etiology of, 345.
chronic, pituitary gland in, 768.
Myopathies pituitary gland in, 773.
Myxœdema, 185.
etiology of, 191.
incomplete, 175.
infantile, 193.
pathogenesis of, 186, 191.
pathology of, 191.
posterior pituitary body in, 514.
symptomatology of, 186.
thyroid gland in, 710.
treatment of, 192.
Myxœdematous idiocy, 197.
infantilism, 201.
diagnosis of, 204.
pathogenesis of, 201.
symptomatology, 201.

Myxœdematous infantilism, treatment of, 206.
Myxœdème fruste, 175.

Narcolepsy in acromegaly, 513.
Nephritin, 784.
Nephritis, acute, 15, 16.
    suprarenal gland in, 16.
  chronic, 15, 16, 17.
    kidney extract in, 784.
    nephritin in, 784.
    suprarenal gland in, 16.
Nerve substance in neurasthenia, 788.
    organotherapy, 788.
Nerve-supply of the adrenals, 54.
Nerves, myelin as source of energy in, 534, 536, 543.
  physiological chemistry of, 532.
Nervous diseases, pituitary gland in, 773.
  energy, source of, 533, 536, 543.
  system, disorders of, 349.
      myelitis, acute, etiology of, 350.
      tabes dorsalis, etiology of, 350.
    somatic center of, 483, 591.
      including neurons, composed of plasma-fibrils surrounded by myelin, 560.
    posterior pituitary body as somatic center of, 591.
Neuralgia, adrenal gland in, 765.
  in acromegaly, 514.
Neurasthenia, brain and nerve substance in, 788.
  cephalopin in, 788.
  pituitary gland in, 773.
  testicular extract in, 782.
  thyroid gland in, 710.
Neuritis, adrenal gland in, 765.
Neuroglia-cells as links between circulation and neurons, 570, 589.
  -fibers as plasma-channels, 540, 543.
  -fibrils of the brain and cord, their capillary supply, 582.
Neuron, circulation of, 539, 559.
  direct continuation of circulation by some of its dendrites, 552.
  functions of gemmules, 577.
  histology of, 518.
  lecithin, the functional ground-substance of, 557.
  lymph-channels of, 586.
  physiological chemistry of, 518, 552.
  physiology of, 519.
  transmission of vibrations between, 579, 581.
  varicosity of, in fatigue and sleep, 522.
Neutrophile leucocytes, 653.
  in assimilation, 654.
Newborn, goiter in the, 272.
Non-toxic hypothyroid goiter, simple, 248.
Numbness in cachectic stage of acromegaly, 514.
Nutrition, leucocytes in, 633.

Obesity, testicular extract in, 782.
  thyroid gland in, 710, 724.
Obstetrics, pituitary gland in, 768.
Old age, functional hypoadrenia of, 88.
    prophylaxis and treatment of, 96.
Oöphorectomy, corpus luteum after, 779.
Opocerebrin in epilepsy, 788.
Opsonin, 31.
Opsonins enhance phagocytosis, how, 696.
  Wright's, thyroparathyroid secretion as, 163.
Optic atrophy in acromegaly, 515.
Orchitic organotherapy, 781.
Organ of Zuckerkandl, 56.
Organic functions, leucocyte in its relation to, 633.
  preparations, fundamental principle of the action of, 700.
Organotherapy, adrenal, 750.
  brain substance, 788.
  corpus luteum, 779.
  internal secretions and, 700.
  kidneys, 782.
  mammary gland, 785.
  nerve substance, 788.
  orchitic, 781.
  ovarian, 776.
  parathyroid, 739.
  pineal gland, 789.
  pituitary, 765.
  testicular, 781.
  thymus, 786.
  thyroid, 708.
Osteomalacia, thyroid gland in, 710.
Osteomyelitis, thyroid gland in, 710.
Ovarian extract, 703, 776.
Ovaries, adrenal secretion in, 478.
Oxidation, thyroparathyroid apparatus in, 143.
Oxidizing substance, action on heart muscle of, 423.

Pachydermia, cretinoid, 197.
Pachymeningitis as a symptom of acromegaly, 515.
Pancreas, diseases of, 348.

- Pancreas, acute pancreatitis, etiology of, 348.
  - functional mechanism of, 381, 385, 420.
  - general function of, 360.
  - in cardiac disorders, 33.
  - in diabetes insipidus, 40.
  - in disease and treatment, 31.
  - in hepatic disorders, 41.
  - in metabolic disorders, 35.
  - in valvular disorders, 33.
  - internal secretion of, 362, 420.
  - relationship between the spleen and, 367.
  - in the formation of glycogen, 361.
- Pancreatitis, acute, etiology, 348.
- Paræsthesia, the posterior pituitary body and, 513, 514.
- Paralysis agitans, parathyroid gland in, 747.
  - testicular extract in, 782.
- Parathyroid gland, 739.
  - tetany, 741.
- Parathyroids, dual function theory of the, 147.
  - effects of the internal secretion of the, 149.
  - functions of the, prevailing views as to the, 143.
  - removal of, 146.
- Parry's disease, 214.
- Pericarditis, 35.
- Peritonitis, 35.
- Phagocytosis, how opsonins enhance, 696.
- Phloridzin and glycosuria, 363.
- Phosphorus as active principle of lecithin, 533.
  - as active principle of myelin, 543.
  - cellular, thyroparathyroid secretion as an oxidation activator on, 152.
  - nervous energy and, 533, 536, 543.
  - posterior pituitary body and, 593.
  - proportion of, in nuclein, 532.
- ierre Marie's disease, 607.
- ineal gland, 789.
  - in backward children, 789.
- ituitary-adrenal nerve, governing center of the adrenals, 71.
- ituitary and glycosuria, 76.
  - bodies as co-centers in sustaining vital processes, 483, 591.
    - phylogeny of, 491.
  - body as the seat of the immunising center, 624.
  - body as the seat of thyroparathyroid center, 168.
  - Pituitary body in mental deficiency, 277.
    - posterior, as an aggregate of neurons, 596.
      - as central sensorium, 593.
      - as general center of nervous system, 483, 511, 591.
      - as somatic center of the nervous system, 591.
      - histology of, 493, 500.
      - physiology of, 493, 591.
  - extract, 704, 765.
- Pituitrin, 767.
- Pleurisy, 35, 346
- Pneumonia, adrenal apoplexy in, 19.
  - pituitary gland in, 770.
  - suprarenal gland in, 19.
  - senile, 12.
    - pituitary gland in, 13.
    - suprarenal gland in, 13.
    - treatment of, 12.
- Polydipsia in acromegaly, 515.
- Polyuria and adrenal insufficiency, 512.
- Post-operative intestinal paralysis, hormone therapy in, 790.
- Progressive hypoadrenia, chronic, 97. (See *Addison's disease.*)
- Progressive hypothyroidia, 185. (See *Myxœdema.*)
- Prurigo, thyroid gland in, 734.
- Pruritus vulvæ of menopause, corpus luteum in, 779.
- Pseudo-Graves's disease, 212.
- Psoriasis, testicular extract in, 782.
  - thyroid gland in, 734, 735.
- Puerperal intoxication, kidney extract in, 784.
- Pulmonary system, innervation of, 454.
- Purpura, adrenal apoplexy in, 19.

- Rachitis. (See *Rickets.*)
- Removal of the parathyroids, 146.
  - of the thyroid, 144.
- Renal disorders and treatment of, 15.
  - adrenals in, 15.
  - anuria, 15.
  - ascites, 17.
  - nephritis, acute, 15, 16.
    - chronic, 15, 16.
  - serous effusions, 17.
  - chronic, adrenal apoplexy in, 20.
  - extract, 703, 782.
- Respiration, nervo-vascular mechanism and, 454.
  - physiology of, 453, 454.
  - pulmonary, adrenal secretion in, 60.
- Respiratory center, identity of, 454.

- Respiratory disorders, adrenal gland in, 761.
  - functions, adrenal secretion and, 453.
  - system, innervation of, 454.
- Rheumatic arthritis, pituitary gland in, 775.
- Rheumatic disorders, 25.
  - pains in acromegaly, 512, 515.
- Rheumatism, 25.
  - spermin in, 782.
  - thyroid gland in, 26.
  - articular, 26.
  - chronic, thyroid gland in, 710, 729.
- Rickets and adrenal insufficiency, 515.
  - fœtal, 305.
  - pituitary gland in, 775.
  - thymus gland in, 787.
  - thyroid gland in, 710.
- Rosacea, hypertrophic, thyroid extract in, 735.

- Sarcoma of the adrenals, 137.
- Scarlatina, suprarenal gland in, 19.
- Scleroderma, thyroid gland in, 735.
- Seborrhœa, thyroid gland in, 735.
- Secretin, 790.
- Senile heart, 9.
  - suprarenal gland in, 10.
  - pneumonia, 12.
    - pituitary gland in, 13.
    - suprarenal gland in, 13.
    - treatment of, 12.
- Sensorium commune, 598.
- Septicemia, suprarenal gland in, 19, 764.
  - thyroid gland in, 738.
- Serous effusions, 17.
  - suprarenal gland in, 17.
- Shock, adrenal gland in, 754, 764.
  - pituitary extract in, 768.
  - removal of adrenals and, 3.
- Skin diseases, thyroid gland in, 734.
- Sleep and cerebral ischemia, 526.
  - retraction of the neuron-gemmules during, 577, 578.
- Spermin, 473, 702, 782.
- Spleen as a leucocytogenic center, 360.
  - functional mechanism, 385, 389.
  - general function of, 359.
  - internal secretion of, 362, 420.
  - relationship between the pancreas and, 367.
- Splenic vein, liver and the, 361.
  - path for spleno-pancreatic secretion, 367.
- Spleno-pancreatic internal secretions, 362, 392, 420.
- Spleno-pancreatic internal secretions, action of, on albuminoid poisons, 369, 392, 405.
- Sporadic cretinism, 197.
- Status hypoparathyreoprivus, 741.
  - parathyreoprivus, 741.
- Sterility, corpus luteum extract in, 780.
- Stigmata of deficient adrenal activity in idiocy, 300.
  - of deficient adrenal cortex activity in idiocy, 300.
  - of deficient thymus activity, 288.
  - of deficient thyroid activity in idiocy, 278.
  - of excessive adrenal cortex activity in idiocy, 301.
- Struma, 243. (See *Goiter.*)
  - gelatinosum, 260.
- Strumitis, 274.
  - prognosis of, 275.
  - symptoms of, 274.
  - treatment of, 275.
- Strychnine poisoning, brain substance in, 788.
- Stunted growth, pituitary in, 773.
- Submersion, adrenal gland in, 764.
- Subsidiary adrenal and interrenal tissues, 55, 57.
- Suprarenal. (See *Adrenal.*)
  - apoplexy, 19, 20.
- Surgical diseases, adrenal gland in, 752.
  - disorders, thyroid gland in, 737.
  - heart-failure, adrenal gland in, 755, 764.
  - septicæmia, adrenal gland in, 764.
- Sweating and adrenal insufficiency, 515.
- Syphilis, spermin in, 782.
  - thyroid gland in, 711.
- Syringomyelia and acromegaly, 514.

- Tabes, testicular extract in, 782.
- Tachycardia, pituitary gland in, 768.
- Temperature, action of, adrenal secretion on, 68.
- Terminal hypoadrenia, 109.
  - pathogenesis of, 110.
  - pathology of, 111.
  - symptomatology of, 110.
  - treatment of, 112.
- Testicles, adrenal secretion in, 473.
- Testicular extract, 702, 781.
  - organotherapy, 702, 780, 782.
- Tetania parathyreopriva, 741.
- Tetanus, brain substance in, 788.
- Tetany, hypoparathyroid, 741.

Tetany, thyroid gland in, 710.
Thymus, deficient activity, stigmata of, 288.
  enlarged, as complicating factor of exophthalmic goiter, 223.
  gland, 786.
  functions of the, 280.
  in mental deficiency, 277.
  stigmata of deficient activity of, 288.
Thyroid activity, deficient, stigmata of, 288.
  apparatus in mental deficiency, 278.
  diseases of, thymus gland in, 786.
  dual function theory of the, 147.
  effects of internal secretion of, 148.
  gland organotherapy, 708.
  functions of the, 143.
  hyperæmia, 206.
    diagnosis of, 209.
    symptomatology of, 207.
    treatment of, 209.
  in its relation to disease and treatment, 20.
    in mental deficiency, 277.
    in mental disorders, 30.
    in pulmonary disorders, 27.
    in rheumatic disorders, 25.
  removal of, 144.
  stigmata of deficient activity in idiocy, 278.
Thyroidism, 212. (See *Hyperthyroidia*.)
Thyroiditis, 206.
  chronic, 209.
Thyroparathyroid apparatus, diseases of the, 174, 212.
    disorders due to deficient activity of the, 174.
    disorders due to excessive activity of the, 212.
    in general oxidation and immunity, 142.
    in immunity, 623.
  center, pituitary body as the seat of, 168.
  problem, 150.
  secretion as activator of cellular phosphorus, 152.
    as Wright's opsonin, 163.
Tic, cephalopin in, 788.
Tonsillitis, infectious, thyroid gland in, 711.
Toxæmia, adrenal gland in, 756, 764.
Toxic albuminoids, reduction of, 369, 402, 420.
  goiter, 258.
Toxins, conversion of, into benign products, 369, 392, 402, 420.
Trypsin as the spleno-pancreatic secretion, 392, 405, 420.
Tuberculosis of bones, thyroid gland in, 737.
  pulmonary, 27.
    adrenal apoplexy in, 20.
    iodine in, 29.
    pituitary gland in, 770.
    thyroid gland in, 711, 737.
    treatment, 29.
Tympanic glands, 56.
Typhoid fever, 18.
    pituitary gland in, 770.
    spermin in, 782.
    suprarenal gland in, 19.
    thyroid gland in, 711.

Urea and its formation, 361.
Urticaria, 24.
Uterine fibroids, mammary gland extract in, 785.
  hæmorrhage, mammary gland extract in, 785.
  involution, mammary gland extract in, 786.

Vaccines, 696.
Vagal system in cardiac functions, 421.
Valvular diseases, etiology of, 345.
Vaporole, 767.
Vasomotor impulses, the posterior pituitary as the source of, 597, 598.
Vital process, the pituitary bodies and, 483, 591.
Volvulus, hormone therapy in, 790.
Vomiting of pregnancy, corpus luteum in, 780.

Wright's opsonin, thyroparathyroid secretion as, 163.

Yellow atrophy of the liver, acute, etiology of, 347.

Zuckerkandl, organ of, 56.

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